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**PATENT APPLICATION**

**TITLE:**

**METHOD FOR TREATING FIBROTIC  
DISEASES OR OTHER INDICATIONS IC**

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**METHOD FOR TREATING FIBROTIC DISEASES OR OTHER INDICATIONS  
IC**

5        This application claims the priority of Serial No. 60/218,273, filed 13-Jul-2000, Serial No. 60/296,435, filed 6-Jun-2001, Serial No. 60/259,242, filed 2-Jan-2001, and Serial No. 60/259,431, filed 29-Dec-2000.

      The present invention relates to methods for treating certain fibrotic diseases or other indications.

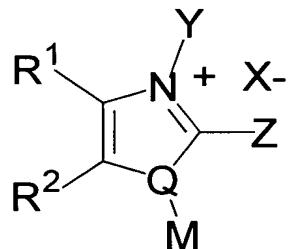
10      Glucose and other sugars react with proteins by a non-enzymatic, post-translational modification process called non-enzymatic glycosylation. At least a portion of the resulting sugar-derived adducts, called advanced glycosylation end products (AGEs), mature to a molecular species that is very reactive, and can readily bind to amino groups on adjacent proteins, resulting in the formation of AGE cross-links  
15      between proteins. Recently a number of classes of compounds have been identified whose members inhibit the formation of the cross-links, or in some cases break the cross-links. These compounds include, for example, the thiazolium compounds described in US Patent No. 5,853,703. As AGEs, and particularly the resulting cross-links, are linked to several degradations in body function linked with diabetes or age, these compounds  
20      have been used, with success, in animal models for such indications. These indications include loss of elasticity in blood vasculature, loss of kidney function and retinopathy.

      Now, as part of studies on these compounds, it has been identified that these compounds inhibit the formation of bioactive agents, such as growth factors and inflammatory mediators, that are associated with a number of indications. These agents  
25      include vascular endothelial growth factor (VEGF) and TGF[ $\beta$ ]. As a result, a number of new indications have been identified for treatment with agents that inhibit the formation of, or more preferably break, AGE-mediated cross-links. It is not unreasonable to infer that the effects seen are due to the removal of AGE-related molecules that provide a stimulus for the production or release of these growth factors.  
30      Removal of such molecules is believed to proceed in part due to the elimination of AGE-related cross-links that lock the AGE-modified proteins in place. Moreover, such compounds also reduce the expression of collagen in conditions associated with excess collagen production. Regardless of the mechanism, now provided are new methods of treating a number of indications.

100-1000-1000-1000

**Summary of the Invention**

In one embodiment, the invention relates to a method of treating or ameliorating or preventing an indication of the invention in an animal, including a human comprising  
5 administering an effective amount of a compound of the formula I:

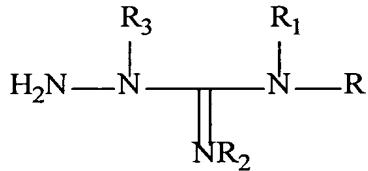


(I)

wherein the substituent groups are defined below. The invention also relates to compounds of formula I.

10 The compounds used in the methods described here are first agents, which are those described with reference to formula I, or second agents, which are aminoguanidine or those compounds described with reference to formula I. The second agents can be used as an adjunct to treatment with a first agent, or as the primary effective agent where noted.

15 Second agents are aminoguanidine or a compound of the aminoguanidine class of formula A



(A)

wherein R is an alkyl group, or a group of the formula  $-N(R^4)(R^5)$  wherein  $R^4$  is hydrogen, and  $R^5$  is an alkyl group or a hydroxyalkyl group; or  $R^4$  and  $R^5$  together with 20 the nitrogen atom are a heterocyclic group containing 4-6 carbon atoms and, in addition to the nitrogen atom, 0-1 oxygen, nitrogen or sulfur atoms;  $R^1$  is hydrogen or an amino group;  $R^2$  is hydrogen or an amino group;  $R^3$  is hydrogen or an alkyl group, wherein R and  $R^1$  cannot both be amino groups. Preferably at least one of  $R^1$ ,  $R^2$ , and  $R^3$  is other than hydrogen. The compounds can be used as their pharmaceutically acceptable acid

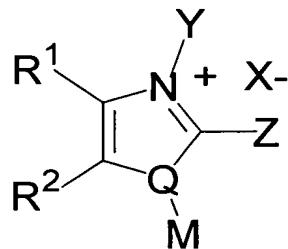
addition salts, and mixtures of such compounds. When aminoguanidine compounds are administered, they can be administered by any route of pharmaceutical administration including those discussed below for other first agents.

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### Detailed Description of the Invention

Provided is a method of treating or ameliorating an indication of the invention in an animal, including a human, comprising administering an effective amount of (A) a compound of the formula I:

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(I)

wherein

a. R<sup>1</sup> and R<sup>2</sup> are

1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy, allyl, amino,  $\omega$ -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, hydroxy, (C<sub>2</sub>-C<sub>6</sub>)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl, Ar {wherein, consistent with the rules of aromaticity, Ar is C<sub>6</sub> or C<sub>10</sub> aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar-alkyl, Ar-O, ArSO<sub>2</sub>-, ArSO-, ArS-, ArSO<sub>2</sub>NH-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-

alkyl)N-C(O)-, or together R<sub>1</sub> and R<sub>2</sub> comprise methylenedioxy [in one embodiment, independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy, allyl,  $\omega$ -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, halo, hydroxy, (C<sub>2</sub>-C<sub>6</sub>)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, Ar {wherein, consistent with the rules of aromaticity, Ar is C<sub>6</sub> or C<sub>10</sub> aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be fused to a benzene, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar-alkyl, Ar-O, ArSO<sub>2</sub>-, ArSO-, ArS-, ArSO<sub>2</sub>NH-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-]; or

2. together with their ring carbons form a C<sub>6</sub>- or C<sub>10</sub>- aromatic fused ring system; or

3. together with their ring carbons form a C<sub>5</sub>-C<sub>7</sub> fused cycloalkyl ring having up to two double bonds including the fused double bond of the -olium or -onium containing ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo substituents [in one embodiment, together with their ring carbons form a C<sub>5</sub>-C<sub>7</sub> fused cycloalkyl ring having up to two double bonds including the fused double bond of the -olium or -onium containing ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, aminocarbonyl, carboxy, fluoro, or oxo substituents]; or

4. together with their ring carbons form a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be optionally substituted with one or more 1-pyrrolidinyl-, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy groups [in one embodiment, together with their ring carbons form a 5- or 6-membered heteroaryl ring,

wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be optionally substituted with one or more halo or (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy groups]; or

5 5. together with their ring carbons form a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and S(O)<sub>n</sub>, where n=0,1, or 2;

**b.** Z is

- 10 1. hydrogen, alkyl, Ar—CH<sub>2</sub>;
2. a group of the formula -NR<sup>3</sup>R<sup>4</sup>, wherein R<sup>3</sup> and R<sup>4</sup> may be independently hydrogen, alkyl, Ar, or Ar—alkyl-;
3. a group of the formula -CH(OR<sup>11</sup>)R<sup>12</sup>, wherein R<sup>11</sup> is hydrogen, methyl, ethyl or CH<sub>3</sub>C(O)-; and R<sup>12</sup> is [C<sub>1</sub> to C<sub>6</sub>]alkyl, Ar, or CO<sub>2</sub>R<sup>13</sup> wherein R<sup>13</sup> is hydrogen methyl or ethyl;
- 15 4. a group of the formula -C(CO<sub>2</sub>R<sup>13</sup>)(OR<sup>11</sup>)R<sup>12</sup>
5. a group of the formula -CH<sub>2</sub>WAr, wherein W is -(C=O)- or -S(O)<sub>n</sub>- where n=1 or 2; or
6. a group of the formula -CH<sub>2</sub>C≡C-R<sup>14</sup>, wherein R<sup>14</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl;

**c.** Y is

- 20 1. amino, or
2. a group of the formula -CH(R<sup>5</sup>)-R<sup>6</sup> wherein
  - (a) R<sup>5</sup> is hydrogen, alkyl-, cycloalkyl-, alkenyl-, alkynyl-, aminoalkyl-, dialkylaminoalkyl-, (N-[C<sub>6</sub> or C<sub>10</sub>]aryl)(N-alkyl)aminoalkyl-, piperidin-1-ylalkyl-, 1-pyrrolidinylalkyl, azetidinylalkyl, 4-alkylpiperazin-1-ylalkyl, 4-alkylpiperidin-1-ylalkyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-ylalkyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-ylalkyl, azetidin-1-ylalkyl, morpholin-4-ylalkyl, thiomorpholin-4-ylalkyl, piperidin-1-ylalkyl, [C<sub>6</sub> or C<sub>10</sub>]aryl, or independently the same as R<sup>6</sup> [in one embodiment, hydrogen or alkyl];
  - (b) R<sup>6</sup> is
    - (1) hydrogen, alkyl (which can be substituted by alkoxy carbonyl), alkenyl, alkynyl, cyano- or Rs, wherein Rs is a C<sub>6</sub> or C<sub>10</sub> aryl or a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

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(2) a group of the formula  $-W-R^7$ , wherein  $R^7$  is alkyl, alkoxy, hydroxy or  $R_s$ , wherein  $W$  is  $-C(=O)-$  or  $-S(O)_n-$  where  $n=1$  or 2;

(3) a group of the formula  $-W-OR^8$  wherein  $R^8$  is hydrogen or alkyl,

(4) a group of the formula  $-CH(OH)R_s$ ; or

(5) a group of the formula  $-W-N(R^9)R^{10}$ , wherein

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[a]  $R^9$  is hydrogen and  $R^{10}$  is an alkyl or cycloalkyl, optionally substituted by

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(i)  $[C_6$  or  $C_{10}]aryl$ , or

(ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more 1-pyrrolidinyl, 4-[ $C_6$  or  $C_{10}]aryl$ piperazin-1-yl, 4-[ $C_6$  or  $C_{10}]aryl$ piperidin-1-yl, azetidin-1-yl, and morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or  $(C_1-C_3)alkylenedioxy$  groups, or fused to a substituted phenyl or pyridine ring, wherein the ring fusion is at a carbon-carbon double bond of the heteroaryl ring [in one embodiment, a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more halo or  $(C_1-C_3)alkylenedioxy$  groups, or fused to a substituted phenyl],

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or

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(iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

[b]  $R^9$  is hydrogen or lower alkyl and  $R^{10}$  is Ar; or

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[c]  $R^9$  is hydrogen or lower alkyl, and  $R^{10}$  is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms are selected from the group consisting of oxygen, nitrogen and sulfur, said heterocycle; or

[d]  $R^9$  and  $R^{10}$  are both alkyl groups; or

[e] R<sup>9</sup> and R<sup>10</sup> together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C<sub>6</sub>-or C<sub>10</sub>)aryl, (C<sub>6</sub>-or C<sub>10</sub>)arylalkyl, or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each such heteroaryl can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy [in one embodiment, R<sup>9</sup> and R<sup>10</sup> together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C<sub>6</sub>-or C<sub>10</sub>)aryl, (C<sub>6</sub>-or C<sub>10</sub>)arylalkyl, or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each such heteroaryl can be optionally substituted with one or more halo or (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy]; or

[f] R<sup>9</sup> and R<sup>10</sup> are both hydrogen; or

d. Q is N, O or S;

e. M is absent when Q is O or S;

f. M is alkyl, vinyl or allyl, or independently the same as Y; and

g. X is a pharmaceutically acceptable anion, or

(B) a pharmaceutically acceptable salt of the compound,

wherein aryl or Ar can be substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy, alkylsulfonyl, alkylsulfinyl,  $\omega$ -alkylenesulfonic acid, alkylthio, allyl, amino, ArC(O)-, ArC(O)NH-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl,

5 dialkylamino, halo, trifluoromethyl, hydroxy, (C<sub>2</sub>-C<sub>6</sub>)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl-, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl [in one embodiment, aryl or Ar can be substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy, alkylsulfonyl, alkylsulfinyl,  $\omega$ -alkylenesulfonic acid, alkylthio, allyl, ArC(O)-, ArC(O)NH-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, halo, trifluoromethyl, hydroxy, (C<sub>2</sub>-C<sub>6</sub>)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid]; and

10 wherein heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, ArC(O)-, ArO-, Ar-, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl [in one embodiment, heterocycles, except those of Ar, can be substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkylsulfonyl, alkylsulfinyl, alkylthio, ArC(O)-, ArO-, Ar-, carboxy, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl].

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In one embodiment, the compound of formula I, is that wherein Y is according to formula -CH(R<sup>5</sup>)R<sup>6</sup>. In another embodiment, the compound of formula I, is that of formula I, wherein Y is according to formula -CH(R<sup>5</sup>)-W-R<sup>7</sup>. In another embodiment, the compound of formula I, is that of formula I, wherein Y is according to formula -CH(R<sup>5</sup>)-W-Rs. In another embodiment, the compound of formula I, is that of formula I, wherein R<sup>1</sup> and R<sup>2</sup> together with their ring carbons form a C<sub>6</sub>- or C<sub>10</sub>- aromatic fused ring which can be substituted by one or more halo, amino, alkyl, sulfonic acid, alkylsulfonyl or  $\omega$ -alkylenesulfonic acid groups, or a C<sub>1</sub>-C<sub>3</sub> alkylenedioxy group with the proviso that when Q is nitrogen R<sup>1</sup> and R<sup>2</sup> do not form a C<sub>6</sub> fused aromatic ring. In another

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embodiment, the compound of formula I, is that of the compound of formula I, wherein Q is S, and Y and Z are both -NH<sub>2</sub>.

**Certain Fibrotic Diseases**

5 Among the indications that can be treated with the invention are a number of indications linked to or associated with the formation of excess collagen. Among these, a number of the indications can be termed fibrotic diseases.

Such fibrotic diseases include systemic sclerosis, mixed connective tissue disease, fibrodysplasia, fibrocystic disease, sarcoidosis, myositis (e.g. polymyositis, 10 primary idiopathic polymyositis, childhood polymyositis, dermatomyositis, childhood dermatomyositis, primary idiopathic dermatomyositis in adults, inclusion body myositis, polymyositis or dermatomyositis associated with malignant tumors). Dermatomyositis can be associated with fibrosing or hypertrophic aspects, including fibrosing alveolitis and pulmonary fibrosis. Treatment using the invention is expected to treat, prevent, 15 reduce or ameliorate such diseases or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases. Amelioration includes reducing the rate of progression of a disease.

Among these fibrotic diseases are diseases that have as a manifestation fibrotic vascular intimal hypertrophy. These diseases include vasculitis (including coronary artery vasculitis), polyarteritis nodosa or temporal arteritis. Treatment using the 20 invention is expected to treat, prevent, reduce or ameliorate vascular intimal hypertrophy in such diseases.

These fibrotic diseases further include diseases that have as a manifestation fibrotic hypertrophy of skin and/or muscle tissue. These diseases include scleroderma, eosinophilic fasciitis, discoid lesions associated with lupus or discoid lupus or surgical 25 adhesions. Treatment using the invention is expected to treat, prevent, reduce or ameliorate such indications or hypertrophy or fibrosis of skin or muscle tissue.

Such fibrotic diseases further include diseases that have as a manifestation fibrotic hypertrophy of nerve tissue. These diseases include cerebrosclerosis, annular sclerosis, diffuse sclerosis and lobar sclerosis. Treatment using the invention is expected 30 to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis of nerve tissue in such diseases.

These fibrotic diseases further include fibrotic lung diseases that have as a manifestation fibrotic hypertrophy or fibrosis of lung tissue. These diseases include

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pulmonary fibrosis (or interstitial lung disease or interstitial pulmonary fibrosis), idiopathic pulmonary fibrosis, the fibrotic element of pneumoconiosis (which is associated with exposure to environmental hazards such as smoking, asbestos, cotton lint, stone dust, mine dust and other particles), pulmonary sarcoidosis, fibrosing 5 alveolitis, the fibrotic or hypertrophic element of cystic fibrosis, chronic obstructive pulmonary disease, adult respiratory distress syndrome and emphysema. Treatment using the invention is expected to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases.

Such fibrotic diseases further include diseases that have as a manifestation 10 fibrotic hypertrophy or fibrosis of prostate, liver, the pleura (e.g., pleurisy, pleural fibrosis) or pancreas. These diseases include benign prostatic hypertrophy (BPH) and fibrosis of the liver. Treatment using the invention is expected to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases.

15 These fibrotic diseases further include diseases that have as a manifestation fibrotic hypertrophy or fibrosis of the bowel wall, such as inflammatory bowel disease, including Crohn's disease. Treatment using the invention is expected to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases.

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**Arteriosclerosis, Atherosclerosis, Stiff Vessel Disease, Peripheral Vascular Disease, Coronary Heart Disease, Stroke, Myocardial Infarct, Cardiomyopathies, Restenosis**

Arteriosclerosis is a disease marked by thickening, hardening, and loss of elasticity in arterial walls, of which atherosclerosis is a sub-type. Arteriosclerosis in turn 25 falls within the genus of stiff vessel diseases. Without limitation to theory, it is believed that damage to the blood vessels of these diseases is due to AGE-caused damage, either through protein cross-linking or the stimulation of bioactive agents, or both. Accordingly, the first agents are used to treat, prevent, reduce or ameliorate stiff vessel disease, including arteriosclerosis and atherosclerosis. Peripheral vascular disease is an 30 indication that overlaps with atherosclerosis but also covers disease which is believed to have a stronger inflammatory component. First agents are used to treat, prevent, reduce or ameliorate peripheral vascular disease. Coronary heart disease is a form of

atherosclerosis of the coronary arteries. First agents are used to treat, prevent, reduce or ameliorate coronary heart disease.

When the heart pumps blood into the vascular system, the ability of the arteries to expand helps to push blood through the body. When arteries become stiff, as they do in 5 the natural process of aging, the ability of the arteries to expand is diminished and also has consequences for the heart. The heart has to work harder to pump the blood into the stiff arteries, and eventually hypertrophies (enlarges in size) to accomplish this. A hypertrophied heart is an inefficient pump, and is one of the disorders that leads to congestive heart failure. One compound believed to work by a mechanism shared by the 10 compounds of the invention, 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt, showed an ability to reverse the stiffness of arteries in a Phase IIa clinical trial, as measured by the ratio of stroke volume (ml) to pulse pressure (mm Hg). The potential clinical benefit of this is to lessen the effort that the heart must expend to push blood throughout the body. The effect is also believed to contribute to preventing hypertrophy 15 and subsequent inefficiency of the heart, which inefficiency would contribute to congestive heart failure.

Stroke is a cardiovascular disease that occurs when blood vessels supplying blood (oxygen and nutrients) to the brain burst or are obstructed by a blood clot or other particle. Nerve cells in the affected area of the brain die within minutes of oxygen 20 deprivation and loss of nerve cell function is followed by loss of corresponding bodily function. Of the four main types of stroke, two are caused by blood clots or other particles. The former two are the most common forms of stroke, accounting for about 70-80 percent of all strokes.

Blood clots usually form in arteries damaged by atherosclerosis. When plaque 25 tears from the sheer forces of blood flowing over an uneven, rigid cap atop the plaque site, thrombotic processes become involved at the "injury" site. As a result, clots can form. First agents are used to prevent, reduce or ameliorate the risk of stroke in patients who have suffered previous strokes or have otherwise been identified as at risk.

First agents can also be used to treat, prevent, reduce or ameliorate peripheral 30 vascular disease and periarticular rigidity.

Treatment with the first agents during the relatively immediate aftermath of a heart attack can be used to reduce the size of the myocardial infarct resulting from the heart attack. This treatment is preferably administered within six hours of the heart

attack, more preferably, within three hours. While the dosages discussed below can be used with this indication, such as a dose of 0.01 - 4.0 mg/kg administered orally or 0.01 - 2.0 mg/kg administered intravenously, preferably within the time period outlined above. Preferred routes of administration include i.v. injection or i.v. drip. Thereafter, optional 5 supplemental administrations can be made with the dosages described below.

Atherosclerosis is a disease that involves deposition of blood lipids in plaque in the arteries throughout the body. In coronary arteries, accumulation of plaque progressively leads to reduced coronary flow, with occlusion of the arteries causing focal death of cardiac tissue (myocardial infarction, heart attack). If the amount of tissue 10 that dies is large enough, death ensues. In a Phase IIa trial, one compound believed to work by a mechanism shared by the compounds of the invention, 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt, increased the amount of circulating triglycerides (lipids). Consistent with the known presence of AGEs in plaque, the result indicates that the agent had a lipid mobilizing effect on arterial plaque. Reducing local deposits of 15 plaque should eventually lessen the risk of myocardial infarction and death due to heart attacks.

Fibrotic diseases further include diseases that have as a manifestation fibrotic hypertrophy of the heart. These diseases include endomyocardial fibrosis (wherein endocardium and subendocardium are fibrosed, such as in some manifestations of 20 restrictive cardiomyopathy), dilated congestive cardiomyopathy (a disorder of myocardial function with heart failure in which ventricular dilation and systolic dysfunction predominate), hypertrophic cardiomyopathy (characterized by marked ventricular hypertrophy with diastolic dysfunction in the absence of an afterload demand), and other cardio-hypertrophies. In dilated congestive cardiomyopathy, 25 typically at presentation there is chronic myocardial fibrosis with diffuse loss of myocytes. In hypertrophic cardiomyopathy, usually the interventricular septum is hypertrophied more than the left ventricular posterior wall (asymmetric septal hypertrophy). Treatment using the invention is expected to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such 30 diseases.

Hypertrophies of the heart can be diagnosed and monitored by methods known in the art, such as by electrocardiogram, echocardiography or magnetic resonance imaging. Such diagnostic methods can be applied in particular for subjects having a risk factor for

such hypertrophy, such as congestive heart failure, prior cardiac surgery or diabetes. In one aspect, the invention comprises identifying cardio-hypertrophy with using biophysical diagnostic tools, and administering an active agent of the invention to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or 5 fibrosis in such diseases. The invention can further include monitoring cardio-hypertrophy during the course of treatment with active agent.

Erosion or tearing of arterial wall plaque can occur due to the rough and irregular shape of the plaque as it forms from deposition of lipids and invasion of cells such as monocytes and macrophages (foam cells). When erosion occurs platelets and other 10 components of the blood clotting system are activated, resulting in formation of a clot (thrombus). When the thrombus grows to such a state that blood flow is reduced, severe angina attacks that characterize unstable angina can occur. Plaque forms irregular shapes and in doing so creates shear stresses from the flow of blood over this irregular form. It is the irregularity of plaque shape that leads to the dislodging or tearing of the plaque, 15 and to the subsequent invasion of reactive cells. On the surface of plaque is collagen, which is believed to contribute to the rigidity of the irregular shape. Without limitation to theory, it is believed that reducing the crosslinking of such a rigid collagen cap results in smoother blood flow, with a reduced risk of angina-causing tears. Accordingly, first agents are used to treat, prevent, reduce or ameliorate unstable angina.

20 Faithful conduction of the electrical impulse from the sinoatrial to the atrioventricular nodes depends upon close apposition of myocardial cells. Excess production of collagen in the heart, which occurs naturally with aging but more so in diabetes and in conditions of heart disorders such as hypertension, causes an increase in the distance between myocardial cells, leading to atrial fibrillation. First agents are used 25 to treat, prevent, reduce or ameliorate atrial fibrillation.

The fibrotic indications further include restenosis, which is the process of increasing artery closure following an operation to open the artery, such as balloon angioplasty.

30 **Bladder Elasticity**

Indications that can be treated, prevented, reduced or ameliorated with the first agents include loss of bladder elasticity. Bladder elasticity is tied to the frequency of urination, and the urgency of desire to urinate. Accordingly, the invention can be used to

treat, prevent, reduce or ameliorate non-obstructive uropathy, a disorder characterized by an overactive bladder that entails increased frequency of urination, a strong and sudden desire to urinate (urgency) which may also be associated with involuntary urinary leakage (urge incontinence).

5

**Macular Degeneration**

The effect of the first agents in reducing levels of other endogenous bioactive agents, particularly VEGF and/or TGF[ $\beta$ ], is believed to underlie effectiveness against macular degeneration or macular edema. Again, however, the invention is not limited to theory. Moreover, an anti-fibrotic effect or another effect against tissue hypertrophy may contribute. Treatment using the invention is expected to treat, prevent, reduce or ameliorate macular degeneration or macular edema. In one aspect of the invention, the treatment is used to treat, prevent, reduce or ameliorate the wet form of macular degeneration. In the wet form, new blood vessel growth has a greater contribution to the disease.

**Amyotrophic lateral sclerosis (ALS)**

ALS is associated with degradations of the motor neuron system and/or the posterior column of the spinal cord. In ALS patients, these structures tend to stain with AGE-reactive antibodies. Treatment using the invention is expected to treat, prevent, reduce or ameliorate ALS.

**Rheumatoid Arthritis, Osteoarthritis, Bone Resorption**

It is believed, without limitation to such theory, that reducing AGE accumulation at the joints affected by rheumatoid arthritis or osteoarthritis reduces stimulation of the production of cytokines involved in inflammatory processes of the disease. Treatment using the invention is expected to treat, prevent, reduce or ameliorate rheumatoid arthritis or osteoarthritis. Similarly, it is believed that reducing AGE accumulation at bone reduces stimulation of bone resorption. Accordingly, the invention is used to treat, prevent, reduce or ameliorate osteoporosis, bone loss or brittle bone.

Dialysis

The first agents can be administered as part of a dialysis exchange fluid, thereby preventing, limiting or ameliorating the damage to tissue caused by the sugars found in such exchange fluid. For example, first agents are expected to prevent, limit or

5 ameliorate the stiffening and sclerosing of peritoneal tissue that occurs in peritoneal dialysis, as well as prevent, limit or ameliorate the formation of new blood vessels in the peritoneal membrane. In hemodialysis, first agents are expected to prevent, limit or ameliorate the stiffening and sclerosing of red blood cells and vasculature resulting from exposure to the sugars exchanged into the blood during dialysis. Exchange fluids for

10 peritoneal dialysis typically contain 10 - 45 g/L of reducing sugar, typically 25 g/L, which causes the formation of AGEs and consequent stiffening and degradation of peritoneal tissue. Similarly, hemodialysis fluids typically contain up to about 2.7 g/L of reducing sugar, typically 1 to 1.8 g/L. Thus, the invention provides methods by which the first agents are provided in these fluids and thereby prevent, limit or ameliorate the

15 damage that would otherwise result. Alternatively, the invention provides methods whereby the first agents are administered by the methods described below to prevent, limit or ameliorate such damage from dialysis. In hemodialysis, the exchange fluid preferably contains 0.006 - 2.3 mg/L of an agent of the invention, more preferably, 0.06 to 1.0 mg/L. In peritoneal dialysis, the exchange fluid preferably contains 0.01 to 24

20 mg/L of an agent of the invention, or preferably, 1.0 to 10 mg/L.

In one embodiment, preventing or ameliorating is effected with a second agent. A preferred route of administration is inclusion in the dialysis fluids. In hemodialysis, the exchange fluid preferably contains 0.125 to 2.5 mg/L of aminoguanidine, more preferably, 0.2 to 1.0 mg/L. In peritoneal dialysis, the exchange fluid preferably contains 1.25 to 25 mg/L of aminoguanidine, or preferably, 2.0 to 10 mg/L. In a preferred aspect of the invention, the first agents are initially administered, and subsequently second agents are used to moderate or limit damage thereafter.

Asthma

30 It is believed, without limitation to such theory, that the first agents or second agents act to prevent, reduce or ameliorate the small but significant thickening of the lung airways associated with asthma. Moreover, the agents are believed to reduce stimulation of the production of cytokines involved in inflammatory processes of the

disease. Accordingly, the agents are used to treat, prevent, reduce or ameliorate asthma. In this embodiment, one preferred route of administration is pulmonary, such as via an aerosol, though peroral administration is also preferred.

5 **Carpal Tunnel Syndrome**

It is believed, without limitation to such theory, that the first agents act to prevent, reduce or ameliorate fibrotic and cytokine-induced elements of carpal tunnel syndrome. Accordingly, the first agents are used to treat, prevent, reduce or ameliorate carpal tunnel syndrome.

10 Fibrotic diseases also include Dupuytren's contracture, a contracture of the palmar fascia often causing the ring and little fingers to bend into the palm. Treatment using the invention is expected to treat, prevent, reduce or ameliorate Dupuytren's contracture, or hypertrophy, fibrotic hypertrophy or fibrosis in Dupuytren's contracture.

In these embodiments, one preferred route of administration is local injection.

15

**Periodontal Disease**

The incidence of periodontal disease is higher in subjects with either insulin-deficient or insulin-resistant diabetes, with consequent hyperglycemia. Again, without limitation to such theory, it is believed that the first agents act to prevent, reduce or ameliorate AGE-induced cytokine action to create or exacerbate periodontal disease. Accordingly, the first or second agents are used to treat, prevent, reduce or ameliorate periodontal disease. In this embodiment, one preferred primary or supplemental route of administration is via mouthwash, or compositions adapted for delivery into the subgingival periodontal pocket (such as implants and erodible microspheres). Peroral administration is again useful. The mouthwash preferably contains 0.003 - 1.0 mg/L of a first agent, more preferably, 0.01 - 0.1 mg/L.

**Sickle Cell Anemia**

It is believed, without limitation to such theory, that the first agents act to prevent, reduce or ameliorate the restraint on blood flow caused by sickling. Again without limitation to theory, the mode of action is believed to be in reducing vascular as well as blood cell inelasticity. Accordingly, the first agents are used to treat, prevent, reduce or ameliorate a sickle cell anemia.

**Erectile Dysfunction**

Fibrotic diseases further include diseases that have as a manifestation fibrotic disease of the penis, including Peyronie's disease (fibrosis of the cavernous sheaths leading to contracture of the investing fascia of the corpora, resulting in a deviated and painful erection). Treatment using the invention is expected to treat, prevent, reduce or ameliorate such diseases, or hypertrophy, fibrotic hypertrophy or fibrosis in such diseases.

Without limitation to theory, it is believed that the first agents act to prevent, reduce or ameliorate inelasticity of tissue of the penis and/or fibrosis of tissue of the penis, such as inelasticity or fibrosis of the cavernous sheaths leading to contracture of the investing fascia of the corpora. At least partial restoration of the resulting inelasticity is believed to facilitate engorgement of the corpora cavernosa with blood. Accordingly, the first agents are used to treat, prevent, reduce or ameliorate erectile dysfunction.

15

**Limited Joint Mobility**

Limited Joint Mobility (LJM) is a disorder associated with diabetes and typically involves the joints of the hands. The fourth and fifth fingers are affected initially by limitation of motion. AGE glycation and crosslinking of tendons (collagen) in the joints is believed to contribute to the disease. It is believed, without limitation to theory, that the first agents act to prevent, reduce or ameliorate inelasticity, fibrous tissue or cytokine-induced inflammation associated with limited joint mobility. Accordingly, the first agents are used to treat, prevent, reduce or ameliorate limited joint mobility.

25 **Antineoplastic Applications**

The first agents inhibit the stimulated formation of bioactive agents, such as VEGF, associated with angiogenesis. Angiogenesis is critical for both normal development and the growth and metastasis of solid tumors. Accordingly, the first agents are used to treat, prevent, reduce or ameliorate the growth of neoplasms by limiting the formation of blood vessels needed to sustain the neoplasms.

**End Stage Renal Disease, Diabetic Nephropathy**

Diabetic Nephropathy is a complication of diabetes that evolves early, typically before clinical diagnosis of diabetes is made. The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels ( $>30$  mg/day or  $20$   $\mu$ g/min) of albumin in the urine (microalbuminuria), followed by albuminuria ( $>300$  mg/24 h or  $\sim 200$   $\mu$ g/min) that develops over a period of 10–15 years. In patients with type 1 diabetes, diabetic hypertension typically becomes manifest early on, by the time that patients develop microalbuminuria. Once overt nephropathy occurs, the glomerular filtration rate (GFR) falls over several years resulting in End Stage Renal Disease (ESRD) in 50% of type 1 diabetic individuals within 10 years and in  $>75\%$  of type 1 diabetics by 20 years of onset of overt nephropathy. Albuminuria (i.e., proteinuria) is a marker of greatly increased cardiovascular morbidity and mortality for patients with either type 1 or type 2 diabetes.

Without limitation to theory, it is believed that damage to the glomeruli and blood vessels of the kidney is due to AGE-caused damage, either through protein cross-linking or the stimulation of bioactive agents, or both. Accordingly, the first agents are used to treat, prevent, reduce or ameliorate damage to kidney in patients at risk for ESRD. The first agents can also be used to treat, prevent, reduce or ameliorate glomerulosclerosis.

20

**Hypertension, Isolated Systolic Hypertension**

Cardiovascular risk correlates more closely with the systolic and the pulse pressure than with the diastolic pressure. In diabetic patients, the cardiovascular risk profile of diabetic patients is strongly correlated to duration of diabetes, glycemic control and blood pressure. Structural matrix proteins contribute to the function of vessels and the heart, and changes in the physical behavior of cardiovascular walls are believed to be important determinants of circulatory function. In elderly individuals, the loss of compliance in the aorta leads to isolated systolic hypertension, which in turn expands the arterial wall and thereby diminishes the dynamic range of elasticity. In vivo studies in rodents, canines and in primates indicate potential utility of 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt in substantially ameliorating vascular stiffening. For example, in a dog model for diabetes, lower end diastolic pressure and increased end diastolic volume, indicators of ventricular elasticity, returned to a value at about the mid-point

between the disease impaired value and the value for control dogs. Treatment with 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt lead to a reduction in the mass of collagen in cardiovascular tissues. In situ hybridization studies demonstrate that 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt reduces the expression of both Type IV

5 collagen and TGF $\beta$ .

Compared with that of a non-diabetic, the diabetic artery is smaller as it is stiffer. As in isolated systolic hypertension in which vessels stiffen with age and lose the dynamic range of expansion under systole. First agents are used to treat, prevent, reduce or ameliorate hypertension, including isolated systolic hypertension and diabetic

10 hypertension. Moreover, the same benefit is anticipated for the more rare hypertensive disorder, pulmonary hypertension. Pulmonary hypertension is a rare blood vessel disorder of the lung in which the pressure in the pulmonary artery (the blood vessel that leads from the heart to the lungs) rises above normal levels and may become life threatening. The similarity in development of elevated blood pressure in the pulmonary

15 bed with the increase in systemic blood pressure in diabetic hypertension and in isolated systolic hypertension suggests similar mechanisms are involved.

Pulse pressure is the difference between systolic and diastolic blood pressure. In a young human, systolic pressure is typically 120 mm Hg and diastolic pressure is 80 mm Hg, resulting in a pulse pressure of 40 mm Hg. With age, in many individuals pulse

20 pressure increases, largely due to the increase in systolic pressure that results from stiff vessel disease. In individuals with pulse pressure greater than 60 mm Hg there is an increased risk of death from cardiovascular morbidities. In a Phase IIa trial, one compound believed to work by a mechanism shared by the compounds of the invention, 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt, reduced pulse pressure in elderly

25 patients with pulse pressures greater than 60 mm Hg in a statistically significant manner. This decrease in pulse pressure was believed to be due primarily to the effect of the agent on lowering the systolic blood pressure.

The agents of the invention are used to treat, prevent, reduce or ameliorate reduced vascular compliance, elevated pulse pressure, and hypertension. Moreover, the

30 agents are used to reduce pulse pressure, increase vascular compliance, or decrease the risk of death.

**Heart Failure**

Congestive Heart Failure (CHF) is a clinical syndrome that entails cardiac disease of the ventricle. Diastolic dysfunction is a subset of heart failure in which the left ventricle stiffens with age. The stiffening of the left ventricle that occurs in CHF and in 5 diastolic dysfunction is believed to result from increased crosslinking of collagen fibers with age and/or fibrosis and related hypertrophy. First agents are used to treat, prevent, reduce or ameliorate heart failure.

**Retinopathy**

10 The effect of diabetes on the eye is called diabetic retinopathy and involves changes to the circulatory system of the retina. The earliest phase of the disease is known as background diabetic retinopathy wherein the arteries in the retina become weakened and leak, forming small, dot-like hemorrhages. These leaking vessels often lead to swelling or edema in the retina and decreased vision. The next stage is 15 proliferative diabetic retinopathy, in which circulation problems cause areas of the retina to become oxygen-deprived or ischemic. New vessels develop as the circulatory system attempts to maintain adequate oxygen levels within the retina. Unfortunately, these new vessels hemorrhage easily. In the later phases of the disease, continued abnormal vessel growth and scar tissue may cause serious problems such as retinal detachment. First 20 agents are used to treat, prevent, reduce or ameliorate diabetic retinopathy. The first agents can be administered by the methods described below, including by topical administration to the eye. The agents can also be administered by intravitreal implant.

**Cataracts, Other damage to Lens Proteins**

25 AGE-mediated crosslinking and/or fibrotic processes are believed to contribute to cataract formation and formation of other damage to lens proteins. First agents are used to treat, prevent, reduce or ameliorate cataracts or other damage to lens proteins.

**Alzheimer's Disease**

30 Considerable evidence exists implicating AGEs that form in the neurofibrillary tangles (tau protein) and senile plaques (beta-amyloid peptide) in early neurotoxic processes of Alzheimer's disease. Insoluble human tau protein is likely crosslinked. Glycation of insoluble tau from AD patients and experimentally AGE-modified tau

generate oxygen free radicals, resulting in the activation of transcription via nuclear factor-kappa B, and resulting in an increase in amyloid beta-protein precursor and release of amyloid beta-peptides. Thus, A.G.E.-modified tau may function as an initiator in a positive feedback loop involving oxidative stress and cytokine gene expression. First 5 agents are used to treat, prevent, reduce or ameliorate Alzheimer's disease.

**Other indications**

For reasons analogous to those set forth above, the invention is believed to be useful in treating, preventing, reducing or ameliorating diabetes or its associated adverse 10 sequelae, and peripheral neuropathy. The agents, especially in topical form, increase elasticity and/or reduce wrinkles in skin. The agents further increase red blood cell deformability.

15 **Combination Therapies**

In cardiovascular therapies, first agents can be administered concurrently or in a combined formulation with one or more antioxidants. Examples of appropriate antioxidants are vitamin A, vitamin B6, vitamin C, vitamin E, glutathione,  $\beta$ -carotene,  $\alpha$ -lipoic acid, coenzyme Q10, selenium and zinc, which are administered in effective 20 amounts as is known in the art. Thus, the invention further provides pharmaceutical compositions comprising an agent of the invention in combination with an effective amount of an antioxidant.

In treating heart failure, cardiomyopathy or heart attack, first agents can be administered concurrently or in a combined formulation with one or more angiotensin 25 converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, calcium channel blockers, diuretics, digitalis or beta blockers. Examples of ACE inhibitors include Captopril, Enalapril, Enalaprilat, Quinapril, Lisinopril and Ramipril, which are administered in effective amounts as is known in the art. Examples of angiotensin II receptor antagonists include Losartan, Irbesartan, Eprosartan, Valsartan and Candesartan, 30 which are administered in effective amounts as is known in the art. Examples of calcium channel blockers include Amlodipine, Bepridil, Diltiazem, Felodipine, Isradipine, Nicardipine, Nifedipine, Nimodipine and Verapamil, which are administered in effective

amounts as is known in the art. Among diuretics, preferred examples include Furosemide, Bumetanide, Torsemide, Ethacrynic acid, Azosemide, Muzolimine, Piretanide, Tripamide and Hydrochlorothiazide, which are administered in effective amounts as is known in the art. Examples of beta adrenergic antagonists include

5 Metoprolol, Carvedilol, Bucindolol, Atenolol, Esmolol, Acebutolol, Propranolol, Nadolol, Timolol, Pindolol, Labetalol, Bopindolol, Carteolol, Penbutolol, Medroxalol, Levobunolol, Bisoprolol, Nebivolol, Celiprolol and Sotalol, which are administered in effective amounts as is known in the art. Thus, the invention further provides pharmaceutical compositions comprising an agent of the invention in combination with

10 an effective amount of an ACE inhibitor, diuretic, digitalis, beta blocker, or combination thereof.

For treating diabetes or complications thereof, the invention further provides pharmaceutical compositions comprising an agent of the invention in combination with an effective amount of a thiazolidinedione or “glitazone” diabetes drug, such as

15 Troglitazone, Rosiglitazone, and Pioglitazone.

In treating atherosclerosis, first agents can be administered concurrently or in a combined formulation with one or more statins (HMG CoA reductase inhibitors) or cholestyramine. Examples of statins include Mevastatin, Lovastatin, Simvastatin, Pravastatin and Fluvastatin, which are administered in effective amounts as is known in

20 the art. Thus, the invention further provides pharmaceutical compositions comprising an agent of the invention in combination with an effective amount of a statin, cholestyramine, or both.

For a number of indications discussed, including sickle cell anemia and diabetic complications, as well as wound healing and any other indication in which increased tissue perfusion is a useful means or adjunct to therapy, the first agents, or aminoguanidine or other agents of the aminoguanidine class can be administered with erythropoietin, which is administered in effective amount as is known in the art. Erythropoietin includes stable forms of erythropoietin such as are marketed by Amgen (Thousand Oaks, CA).

30 For all indications, first agents can be administered concurrently or in a combined formulation with aminoguanidine or other agents of the aminoguanidine class, which are administered in effective amounts as is known in the art.

The method of the invention is used to treat animals, preferably mammals, preferably humans.

In accordance with the present invention, methods for administering pharmaceutical compositions containing certain compounds have been developed for 5 treating the indications described. These agents are either substituted thiazolium, oxazolium, or imidazolium agents as shown in the Summary section above.

Pharmaceutical compositions of the invention include administering an effective amount of a compound of the formula I.

The alkyl, and alkenyl groups referred to below include both C1 to C6 linear and 10 branched alkyl and alkenyl groups, unless otherwise noted. Alkoxy groups include linear or branched C1 to C6 alkoxy groups, unless otherwise noted.

“Ar” (consistent with the rules governing aromaticity) refers to a C<sub>6</sub> or C<sub>10</sub> aryl, or a 5 or 6 membered heteroaryl ring. The heteroaryl ring contains at least one and up to three atoms of N for the 6 membered heteroaryl ring. The 5 membered heteroaryl ring 15 contains; (1) from one to three atoms of N, or (2) one atom of O or S and zero to two atoms of N. The aryl or heteroaryl is optionally substituted as set forth below.

Nonlimiting examples of heteroaryl groups include: pyrrolyl, furanyl, thienyl, pyridyl, oxazolyl, pyrazolyl, pyrimidinyl, and pyridazinyl.

“Ar” can be fused to either a benzene, pyridine, pyrimidine, pyridazine, or (1,2,3) 20 triazine ring.

“Rs” refers to a C<sub>6</sub> or C<sub>10</sub> aryl group (optionally substituted as set forth below) or a heterocycle containing 4-10 ring members and 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur (wherein said heterocycle is optionally substituted as set forth below). Where Rs is a non aromatic heterocycle containing sulfur 25 atom as ring members, the sulfur atoms can exist in various oxidation states, as S(O)<sub>n</sub>, where n is 0,1, or 2.

As used herein, C<sub>6</sub> or C<sub>10</sub> aryl groups and heterocycles containing 4 to 10 ring members are monocyclic or bicyclic. The ring fusions of the bicyclic heterocycles are at carbon-carbon bonds.

30 In certain embodiments of the invention, the thiazoliums, imidazoliums, and oxazoliums of the invention contain R<sup>1</sup> and R<sup>2</sup> substitutions that together with their ring carbons (the C4-C5 carbons of the thiazoliums, imidazoliums, and oxazoliums) form a fused C5 to C7 cycloalkyl ring having up to two double bonds including the fused double

bond (the C4-C5 double bond of the thiazoliums, imidazoliums, and oxazoliums). The cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxy carbonyl, amino, aminocarbonyl, carboxy, fluoro, and oxo substituents. One of ordinary skill in the art will recognize that where cycloalkyl groups contain double bonds, the  $sp^2$  hybridized carbon atoms can contain only one substituent (which can not be amino- or oxo-).  $sp^3$  hybridized carbon atoms in the cycloalkyl ring can be geminally substituted with the exception that (1) two amino groups and (2) one amino and one fluoro group can not be substituted on the same  $sp^3$  hybridized carbon atom.

In certain embodiments of the invention, the thiazoliums, imidazoliums, and oxazoliums of the invention contain  $R^1$  and  $R^2$  substitutions that together with their ring carbons (the C4-C5 carbons of the thiazoliums, imidazoliums, and oxazoliums) form a five to eight membered heterocycle (i.e. a bicyclic heterocycle is formed). In these embodiments the heterocycle is preferably not aromatic. Particular compounds within these embodiments contain sulfur atoms in the ring fused to the thiazoliums, imidazoliums, and oxazoliums. These sulfur atoms in these particular compounds can exist in various oxidation states, as  $S(O)_n$ , where  $n$  is 0, 1, or 2.

In certain embodiments of the invention, the thiazoliums, imidazoliums, and oxazoliums of the invention contain  $R^1$  and  $R^2$  substitutions that together with their ring carbons (the C4-C5 carbons of the thiazoliums, imidazoliums, and oxazoliums) form a five or six membered heteroaryl ring (i.e., a bicyclic aromatic heterocycle is formed). A preferred bicyclic aromatic heterocycle of the invention is a purine analog [Q is N and  $R^1$  and  $R^2$  together with their ring carbons (the C4 and C5 of the imidazolium ring) form a pyrimidine ring].

In certain embodiments, the thiazoliums, imidazoliums, and oxazoliums of the invention contain a Y group which can be  $-CH(R^5)-R^6$ . In those embodiments where  $R^5$  is alkenyl, preferably alkenyl is  $-C=C-R^E$ , where  $R^E$  is alkyl, H, or hydroxy( $C_1-C_6$ )alkyl. In those embodiments wherein  $R^5$  is alkynyl, preferably alkynyl is  $-C\equiv C-R^F$ , where  $R^F$  is alkyl, hydrogen, or hydroxy( $C_1-C_6$ )alkyl.

Aryl or Ar, can generally be substituted with, in addition to any substitutions specifically noted one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkylamino, ( $C_1-C_3$ )alkylenedioxy, alkylsulfonyl [alkylS(O)<sub>2</sub>], alkylsulfinyl [alkylS(O)-],  $\omega$ -alkylenesulfonic acid [-alkylSO<sub>3</sub>H where

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n=1-6)], alkylthio, allyl, amino, ArC(O)-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C2-C6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid [-SO<sub>3</sub>H], 1-pyrrolidinyl-, 4-[C6 or C10]arylpiperazin-1-yl-, 4-[C6 or C10]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, 5 and piperidin-1-yl.

Heterocycles, except those of Ar, can generally be substituted with acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, alkylsulfonyl [alkylS(O)<sub>2</sub>-], alkylsulfinyl [alkylS(O)-], alkylthio, amino, ArC(O)-, ArO-, Ar-, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl. Preferably multiple substituents are located on different atoms of the heterocyclic ring, with the proviso that alkyl, alkylcarbonyl, and fluoro substituents can be substituted on the same carbon atom of the heterocyclic ring. Heterocycles can be substituted with one or more substituents.

The halo atoms can be fluoro, chloro, bromo or iodo. Chloro and fluoro are 15 preferred for aryl substitutions.

For the purposes of this invention, the compounds of formula (I) are formed as biologically or pharmaceutically acceptable salts. Useful salt forms include the halides (particularly bromides and chlorides), tosylates, methanesulfonates, brosylates, fumarates, maleates, succinates, acetates, mesitylenesulfonates, and the like. Other 20 related salts can be formed using similarly non-toxic, and biologically or pharmaceutically acceptable anions.

Representative, non-limiting examples of compounds of the present invention are:

3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]thiazolium bromide  
25 3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide  
3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide  
3-[2-[4-(2-ethoxy-2-oxoethyl)-2-thiazolyl]amino-2-oxoethyl]-4,5-dimethylthiazolium chloride  
30 3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4-methyl-5-(6-hydroxyhexyl)thiazolium bromide  
3-[2-(2,6-dimethyl-4-morpholinyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide  
3-(2-(1-piperidinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-(2-(2-furanyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-(2-(2-furanyl)-2-oxoethyl)-4-(2-hydroxypentyl)thiazolium bromide

3-[2-(2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide

5      3-(2-(1-pyrrolidinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-[2-(3-methyl-2-thianaphthenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide

3-[2-(4-phenyl-1-piperazinyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide

3-(2-(2-thienyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-(2-(2-thienyl)-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide

10     3-(2-(4-thiomorpholiny)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-(2-(hexahydro-1-azepinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-[2-(4-[2-methoxyphenyl]-1-piperazinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride

15     3-(2-(octahydro-1-azocinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-(2-(2-pyridinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-[2-(2-methyl-1-piperidinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride

3-[2-(2,6-dimethyl-1-piperidinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride

3-[2-(4-benzyl-1-piperidinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride

3-[2-(4-benzyl-1-piperazinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride

20     3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4-octylthiazolium bromide

3-(2-(4-morpholiny)-2-oxoethyl)-4,5-dimethylthiazolium bromide

3-[2-[4-(2-ethoxy-2-oxoethyl)-2-thiazolyl]amino-2-oxoethyl]-4,5-dimethylthiazolium chloride

25     3-(2-(4-morpholiny)-2-oxoethyl)-4,5-dioctadecylthiazolium bromide

3-[2-(2,6-dimethyl-4-morpholiny)-2-oxoethyl]-4,5-dipentylthiazolium bromide

3-(2-(1-piperidinyl)-2-oxoethyl)-4,5-didodecylthiazolium bromide

3-(2-(2-furanyl)-2-oxoethyl)-5-decylthiazolium bromide

3-[2-(2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)-2-oxoethyl]-4,5-dioctylthiazolium bromide

30     3-(2-(1-pyrrolidinyl)-2-oxoethyl)-4,5-diethylthiazolium bromide

3-[2-(3-methyl-2-thianaphthenyl)-2-oxoethyl]-4,5-dipentylthiazolium bromide

3-[2-(4-phenyl-1-piperazinyl)-2-oxoethyl]thiazolium bromide

3-(2-(2-thienyl)-2-oxoethyl)thiazolium bromide

3-(2-(2-thienyl)-2-oxoethyl)-4-methyl-5-(6-hydroxyhexyl)thiazolium bromide  
3-(2-(4-thiomorpholinyl)-2-oxoethyl)thiazolium bromide  
3-(2-(hexahydro-1-azepinyl)-2-oxoethyl)-4,5-dioctylthiazolium bromide  
3-(2-(octahydro-1-azocinyl)-2-oxoethyl)-4,5-didecylthiazolium bromide  
5 3-(2-(2-pyridinyl)-2-oxoethyl)-4,5-dioctylthiazolium bromide  
3-[2-(2-methyl-1-piperidinyl)-2-oxoethyl]-4,5-dipropylthiazolium chloride  
3-[2-(2,6-dimethyl-1-piperidinyl)-2-oxoethyl]-4-methylthiazolium chloride  
3-[2-(4-benzyl-1-piperidinyl)-2-oxoethyl]-5-methylthiazolium chloride  
3-[2-(4-benzyl-1-piperazinyl)-2-oxoethyl]-4-octylthiazolium chloride  
10 3-aminothiazolium mesitylenesulfonate;  
3-amino-4,5-dimethylaminothiazolium mesitylenesulfonate;  
2,3-diaminothiazolinium mesitylenesulfonate;  
3-(2-methoxy-2-oxoethyl)thiazolium bromide;  
3-(2-methoxy-2-oxoethyl)-4,5-dimethylthiazolium bromide;  
15 3-(2-methoxy-2-oxoethyl)-4-methylthiazolium bromide;  
3-(2-phenyl-2-oxoethyl)-4-methylthiazolium bromide;  
3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium bromide;  
3-amino-4-methylthiazolium mesitylenesulfonate;  
3-(2-methoxy-2-oxoethyl)-5-methylthiazolium bromide;  
20 3-(3-(2-phenyl-2-oxoethyl)-5-methylthiazolium bromide;  
3-[2-(4-bromophenyl)-2-oxoethyl] thiazolium bromide;  
3-[2-(4-bromophenyl)-2-oxoethyl]-4-methylthiazolium bromide;  
3-[2-(4-bromophenyl)-2-oxoethyl]-5-methylthiazolium bromide;  
3-[2-(4-bromophenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;  
25 3-(2-methoxy-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;  
3-(2-phenyl-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;  
3-[2-(4-bromophenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium  
bromide;  
3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide;  
30 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide;  
3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride;  
3-(2-methoxy-2-oxoethyl)benzothiazolium bromide;  
3-(2-phenyl-2-oxoethyl)benzothiazolium bromide;

3-[2-(4'-bromophenyl)-2-oxoethyl]benzothiazolium bromide;  
3-(carboxymethyl)benzothiazolium bromide;  
2,3-(diamino)benzothiazolium mesylenesulfonate;  
3-(2-amino-2-oxoethyl)thiazolium bromide;  
5 3-(2-amino-2-oxoethyl)-4-methylthiazolium bromide;  
3-(2-amino-2-oxoethyl)-5-methylthiazolium bromide;  
3-(2-amino-2-oxoethyl)-4,5-dimethylthiazolium bromide;  
3-(2-amino-2-oxoethyl)benzothiazolium bromide;  
3-(2-amino-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;  
10 3-amino-5-(2-hydroxyethyl)-4-methylthiazolium mesylenesulfonate;  
3-(2-methyl-2-oxoethyl)thiazolium chloride;  
3-amino-4-methyl-5-(2-acetoxyethyl)thiazolium mesylenesulfonate;  
3-(2-phenyl-2-oxoethyl)thiazolium bromide;  
3-(2-methoxy-2-oxoethyl)-4-methyl-5-(2-acetoxyethyl)thiazolium bromide;  
15 3-(2-amino-2-oxoethyl)-4-methyl-5-(2-acetoxyethyl)thiazolium bromide;  
2-amino-3-(2-methoxy-2-oxoethyl)thiazolium bromide;  
2-amino-3-(2-methoxy-2-oxoethyl)benzothiazolium bromide;  
2-amino-3-(2-amino-2-oxoethyl)thiazolium bromide;  
20 2-amino-3-(2-amino-2-oxoethyl)benzothiazolium bromide;  
3-[2-(4-methoxyphenyl)-2-oxoethyl]thiazolium bromide;  
3-[2-(2,4-dimethoxyphenyl)-2-oxoethyl]thiazolium bromide;  
3-[2-(4-fluorophenyl)-2-oxoethyl]thiazolium bromide;  
3-[2-(2,4-difluorophenyl)-2-oxoethyl]thiazolium bromide;  
3-[2-(4-diethylaminophenyl)-2-oxoethyl]thiazolium bromide;  
25 3-propargylthiazolium bromide;  
3-propargyl-4-methylthiazolium bromide;  
3-propargyl-5-methylthiazolium bromide;  
3-propargyl-4,5-dimethylthiazolium bromide;  
3-propargyl-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;  
30 3-(2-[3-methoxyphenyl]-2-oxoethyl)thiazolium bromide;  
3-(2-[3-methoxyphenyl]-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;  
3-(2-[3-methoxyphenyl]-2-oxoethyl)-benzothiazolium bromide;

2,3-diamino-4-chlorobenzothiazolium mesitylenesulfonate;  
2,3-diamino-4-methylthiazolium mesitylenesulfonate;  
3-amino-4-methyl-5-vinylthiazolium mesitylenesulfonate;  
2,3-diamino-6-chlorobenzothiazolium  
5 2,6-diamino-benzothiazole dihydrochloride;  
2,6-diamino-3-[2-(4-methoxyphenyl)-2-oxoethyl]benzothiazolium bromide;  
2,6-diamino-3-[2-(3-methoxyphenyl)-2-oxoethyl]benzothiazolium bromide;  
2,6-diamino-3-[2-(4-diethylaminophenyl)-2-oxoethyl]benzothiazolium bromide;  
2,6-diamino-3-(2-(4-bromophenyl)-2-oxoethyl] benzothiazolium bromide;  
10 2,6-diamino-3-[2-(2-phenyl)-2-oxoethyl] benzothiazolium bromide;  
2,6-diamino-3-[2-(4-fluorophenyl-2-oxoethyl] benzothiazolium bromide;  
3-acetamido-4-methyl-5-thiazolyl-ethyl acetate mesitylenesulfonate;  
2,3-diamino-5-methylthiazolium mesitylenesulfonate;  
3-[2-(2-naphthyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)-thiazolium bromide;  
15 3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;  
3-[2-(2,6-dichlorophenethylamino)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;  
3-[2-dibutylamino-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;  
20 3-[2-(4-carbethoxyanilino)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;  
3-(2-(2,6-diisopropylanilino)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;  
3-amino-4-methyl-5-[2-(2,6-dichlorobenzyl)oxyethyl]thiazolium  
25 mesitylenesulfonate;  
3-[2-(4-carbmethoxy-3-hydroxyanilino)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;  
2,3-diamino-4,5-dimethylthiazolium mesitylene sulfonate;  
2,3-diamino-4-methyl-5-(2-hydroxyethyl)thiazolium mesitylene sulfonate;  
30 2,3-diamino-5-(3,4-trimethylenedioxy phenyl)-thiazolium mesitylene sulfonate;  
3-[2-(1,4-benzodioxan-6-yl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-[2-(3,4-trimethylenedioxyphenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-(2-[3,4-benzodioxan-6-yl]-2-oxoethyl)thiazolium bromide;

3-[2-(3,4-trimethylenedioxyphenyl)-2-oxoethyl]thiazolium bromide;

5 3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]thiazolium bromide;

3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-4-methylthiazolium bromide;

3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-5-methylthiazolium bromide;

10 3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-benzothiazolium bromide;

1-methyl-3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]imidazolium bromide;

15 3-[2-(4-n-pentylphenyl)-2-oxoethyl]thiazolium bromide;

3-[2-(4-n-pentylphenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-[2-(4-diethylaminophenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

20 3-(2-phenyl-2-oxoethyl)-4-methyl-5-vinylthiazolium bromide;

3-[2-(3,5-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-4-methyl-5-vinylthiazolium bromide;

3-(2-tert-butyl-2-oxoethyl)thiazolium bromide

3-(2-tert-butyl-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

25 3-(3'-methoxybenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium chloride;

3-(2,6-dichlorobenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium chloride;

3-(2-nitrobenzyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-[2-(4-chlorophenyl)-2-oxoethyl]thiazolium bromide;

3-[2-(4-chlorophenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

30 3-[2-(4-methoxyphenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]thiazolium bromide

3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide  
 3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide  
 3-[2-[4-(2-ethoxy-2-oxoethyl)-2-thiazolyl]amino-2-oxoethyl]-4,5-  
 5 dimethylthiazolium chloride  
 3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4-methyl-5-(6-  
 hydroxyhexyl)thiazolium bromide  
 3-[2-(2,6-dimethyl-4-morpholinyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide  
 3-(2-(1-piperidinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide  
 10 3-(2-(2-furanyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide  
 3-(2-(2-furanyl)-2-oxoethyl)-4-(2-hydroxypentyl)thiazolium bromide  
 3-[2-(2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide  
 15 3-(2-(1-pyrrolidinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide  
 3-[2-(3-methyl-2-thianaphthetyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide  
 3-[2-(4-phenyl-1-piperazinyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide  
 3-(2-(2-thienyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide  
 3-(2-(2-thienyl)-2-oxoethyl)-4-methyl-5-hydroxyethylthiazolium bromide  
 3-(2-(4-thiomorpholinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide  
 20 3-(2-(hexahydro-1-azepinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide  
 3-[2-(4-[2-methoxyphenyl]-1-piperazinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride  
 3-(2-(octahydro-1-azocinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide  
 3-(2-(2-pyridinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide  
 25 3-[2-(2-methyl-1-piperidinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride  
 3-[2-(2,6-dimethyl-1-piperidinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride  
 3-[2-(4-benzyl-1-piperidinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride  
 3-[2-(4-benzyl-1-piperazinyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride  
 3-[2-(3-phenyl-5-isoxazolyl)-2-oxoethyl]-4-octylthiazolium bromide  
 30 3-(2-(4-morpholinyl)-2-oxoethyl)-4,5-dimethylthiazolium bromide  
 3-[2-[4-(2-ethoxy-2-oxoethyl)-2-thiazolyl]amino-2-oxoethyl]-4,5-  
 dipropylthiazolium chloride  
 3-(2-(4-morpholinyl)-2-oxoethyl)-4,5-dioctadecylthiazolium bromide

3-[2-(2,6-dimethyl-4-morpholinyl)-2-oxoethyl]-4,5-dipentylthiazolium bromide  
 3-(2-(1-piperidinyl)-2-oxoethyl)-4,5-didodecylthiazolium bromide  
 3-(2-(2-furanyl)-2-oxoethyl)-5-decylthiazolium bromide  
 3-[2-(2-oxo-1,2,3,4-tetrahydro-6-quinolinyl)-2-oxoethyl]-4,5-dioctylthiazolium  
 5 bromide  
 3-(2-(1-pyrrolidinyl)-2-oxoethyl)-4,5-diethylthiazolium bromide  
 3-[2-(3-methyl-2-thianaphthyl)-2-oxoethyl]-4,5-dipentylthiazolium bromide  
 3-[2-(4-phenyl-1-piperazinyl)-2-oxoethyl]thiazolium bromide  
 3-(2-(2-thienyl)-2-oxoethyl)thiazolium bromide  
 10 3-(2-(2-thienyl)-2-oxoethyl)-4-methyl-5-(6-hydroxyhexyl)thiazolium bromide  
 3-(2-(4-thiomorpholinyl)-2-oxoethyl)thiazolium bromide  
 3-(2-(hexahydro-1-azepinyl)-2-oxoethyl)-4,5-dioctylthiazolium bromide  
 3-(2-(octahydro-1-azocinyl)-2-oxoethyl)-4,5-didecylthiazolium bromide  
 3-(2-(2-pyridinyl)-2-oxoethyl)-4,5-dioctylthiazolium bromide  
 15 3-[2-(2-methyl-1-piperidinyl)-2-oxoethyl]-4,5-dipropylthiazolium chloride  
 3-[2-(2,6-dimethyl-1-piperidinyl)-2-oxoethyl]-4-methylthiazolium chloride  
 3-[2-(4-benzyl-1-piperidinyl)-2-oxoethyl]-5-methylthiazolium chloride  
 3-[2-(4-benzyl-1-piperazinyl)-2-oxoethyl]-4-octylthiazolium chloride  
 1-methyl-3-[2-(3-methoxyphenyl)-2-oxoethyl]imidazolium bromide;  
 20 1-methyl-3-[2-(4-methoxyphenyl)-2-oxoethyl]imidazolium bromide;  
 1-methyl-3-[2-(2,4-dimethoxyphenyl)-2-oxoethyl]imidazolium bromide;  
 1-methyl-3-[2-(4-diethylaminophenyl)-2-oxoethyl]imidazolium bromide;  
 1-methyl-3-[2-amino-2-oxoethyl]imidazolium bromide;  
 1-methyl-2-amino-imidazolium mesitylene sulfonate;  
 25 1-methyl-3-[2-phenyl-2-oxoethyl]imidazolium bromide;  
 3-amino-1-(ethoxycarbonylpentyl)imidazolium mesitylenesulfonate;  
 1-(ethoxycarbonylpentyl)-3-[2-(3-methoxyphenyl)-2-oxoethyl]imidazolium  
 bromide;  
 1-methyl-3-[2-(4-bromophenyl)-2-oxoethyl]imidazolium bromide;  
 30 1-methyl-3-[2-(4-fluorophenyl)-2-oxoethyl]imidazolium bromide;  
 1-methyl-3-[2-(3,4-difluorophenyl)-2-oxoethyl]imidazolium bromide;  
 1-(ethoxycarbonylpentyl)-3-[2-(4-methoxyphenyl)-2-oxoethyl]imidazolium  
 bromide;

1-(4-acetylphenyl)-3-amino-imidazolium mesitylenesulfonate;  
1-(ethoxycarbonylpentyl)-3-[2-(4-methoxyphenyl)-2-oxoethyl]imidazolium bromide;  
1-(ethoxycarbonylpentyl)-3-[2-(4-methylphenyl)-2-oxoethyl]imidazolium bromide;  
5   bromide;  
      1-amino-3-benzoyl-imidazolium mesitylene sulfonate;  
      1-methyl-3-(2-naphth-2-yl-2-oxoethyl)imidazolium bromide;  
      1-methyl-3-[(4-biphen-1-yl)-2-oxoethyl]imidazolium bromide;  
      1-methyl-3-[(3-trifluoromethylphenyl)-2-oxoethyl]imidazolium bromide;  
10   1-methyl-3-[4-(2,4-difluorophenyl)-2-oxoethyl]imidazolium chloride;  
      3-[2-(thien-2-yl)-2-oxoethyl]-1-methyl-5-imidazolium bromide;  
      1-methyl-3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]imidazolium bromide;  
      1-methyl-3-[2-(2,4-dichlorophenyl)-2-oxoethyl]imidazolium chloride;  
      3-(2-phenyl-2-oxoethyl)-1-phenylimidazolium chloride;  
15   3-(2-phenyl-2-oxoethyl)-1-ethylimidazolium chloride;  
      3-(2-phenyl-2-oxoethyl)-1-butylimidazolium chloride;  
      3-(2-phenyl-2-oxoethyl)-1-allylimidazolium chloride;  
      3-(2-trifluoromethylphenyl-2-oxoethyl)-4,5-dimethylthiazolium bromide;  
      3-(2-trifluoromethylphenyl-2-oxoethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium  
20   bromide;  
      3-(2-trifluoromethylphenyl-2-oxoethyl)-1-methylimidazolium bromide;  
      3-(2-trifluoromethylphenyl-2-oxoethyl)-1-methylimidazolium bromide;  
      1-butyl-3-amino-imidazolium-mesitylenesulfonate;  
      3-[2-(thien-2-yl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
25   3-[2-(pyrrolidin-1-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
      3-(2-phenyl-2-oxoethyl)-1,2-dimethylimidazolium chloride;  
      3-amino-1,2-dimethylimidazolium mesitylenesulfonate;  
      3-[2-(pyrrolidin-1-yl)-2-oxoethyl]-1-ethylimidazolium chloride;  
      3-[2-(pyrrolidin-1-yl)-2-oxoethyl]-1-phenylimidazolium chloride;  
30   3-[2-(pyrrolidin-1-yl)-2-oxoethyl]-1-methylimidazolium chloride;  
      3-[2-(thien-2-yl)-2-oxoethyl]-1-ethylimidazolium bromide;  
      3-[2-(thien-2-yl)-2-oxoethyl]-1-phenylimidazolium bromide;  
      3-[2-(thien-2-yl-2-oxoethyl)-1,4,5-trimethylimidazolium bromide;

3-[2-(pyrrolidin-2-yl)-2-oxoethyl]-1,4,5-trimethylimidazolium chloride;  
3-[2-(4-chlorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(4-bromophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(4-fluorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
5 3-[2-(2,4-difluorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-(2,4-dichlorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-(3,4-difluorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(2-methoxyphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(3-methoxyphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
10 3-[2-(4-methoxyphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(2,4-dimethoxyphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(2,5-dimethoxyphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(4-methylphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
15 3-[2-(4-diethylaminophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-amino-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-oxoethyl]-1,2-dimethyl-imidazolium  
bromide;  
3-[2-(3,4-trimethylenedioxyphenyl)-2-oxoethyl]-1,2-dimethyl-imidazolium  
20 bromide;  
3-[2-(4-biphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(3,5-dichloroanilino)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(4-trifluoromethylphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(2,6-dichlorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
25 3-[2-(thiomorpholin-4-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-(morpholin-4-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-(piperidin-1-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-hexamethyleneimino-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-heptamethyleneimino-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
30 3-[2-naphthyl-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(2-trifluoromethylphenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(2-trifluoromethylphenyl)-2-oxoethyl]-2,4,5-trimethylthiazolium bromide;  
3-(2-methyl-2-oxoethyl)-1,2-dimethylimidazolium chloride;

3-(2-phenyl-2-oxoethyl)-2-amino-1-methylbenzimidazolium chloride;

3-[2-(thiomorpholin-4-yl)-2-oxoethyl]-1-methylimidazolium chloride;

3-[2-(4-phenylpiperazin-1-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(4-benzylpiperazin-1-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

5 3-[2-{6-(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-naphthalyl)}-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-(1,4-benzodioxan-6-yl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-(phenyl)-2-oxoethyl]-5-chloro-3-methyl-1-ethylimidazolium chloride;

3-[2-(phenyl)-2-oxoethyl]-4-methyl-2-ethylthiazolium chloride;

10 3-(2-phenyl-2-oxoethyl)-1-methyl-2-aminoimidazolium chloride;

3-[2-(pyrrolidin-2-yl)-2-oxoethyl]-2-amino-1-methylimidazolium chloride;

3-(2-phenyl-2-oxoethyl)-1,2-dimethyl-5-nitroimidazolium chloride;

3-[2-(4-acetylanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(4-carboethoxyanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

15 3-[2-(2,6-diisopropylanilino)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-anilino-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[(4-bromoanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(4-[morpholin-4-yl]phenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-dibutylamino-2-oxoethyl]-1,2-dimethylimidazolium chloride;

20 3-[2-(2,6-dichloro-phenethylamino)-2-oxoethyl]-1,2-dimethylimidazolium;

3-[2-(3-hydroxy-4-methoxycarbonylanilino)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

3-[2-cyclopentylamino-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-neopentylamino-2-oxoethyl]-1,2-dimethylimidazolium chloride;

25 3-[2-(pyridin-2-yl)-2-oxoethyl]-4,5-dimethylimidazolium bromide;

3-(2-phenyl-2-oxoethyl)-1,4,5-trimethylimidazolium chloride;

3-(2-phenyl-2-oxoethyl)-1,2,4,5-tetramethylimidazolium chloride;

3-[2-(6-[1,2,3,4-tetrahydroquinolinyl])-2-oxoethyl]-1,2-dimethylimidazolium chloride;

30 3-[2-(2,6-difluorophenyl)-2-oxoethyl]-1,2-dimethylimidazolium bromide;

1-vinyl-3-[2-phenyl-2-oxoethyl]imidazolium chloride;

1-(4-hydroxyphenyl)-3-(2-phenyl-oxoethyl)imidazolium chloride;

1-(4-acetylphenyl)-3-(2-phenyl-2-oxoethyl)imidazolium chloride;

1-methyl-3-(2-phenyl-2-oxoethyl)benzimidazolium chloride;  
1,5-dicyclohexyl-3-(2-phenyl-2-oxoethyl)imidazolium chloride;  
1-(4-methoxycarbonylphenyl)-3-(2-phenyl-2-oxoethyl)imidazolium chloride;  
1-benzyl-3-(2-phenyl-2-oxoethyl)imidazolium chloride;  
5 1-(4-methoxyphenyl)-3-(2-phenyl-2-oxoethyl)imidazolium chloride;  
3-[2-(tert-butylamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-(2,4-difluoroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-(2,4,6-trimethylanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-(2-cyclohexylamino-2-oxoethyl)-1,2-dimethylimidazolium chloride;  
10 3-[2-(4-carboxy-3'-hydroxyanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-([2-morpholin-4-yl]ethylamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-(3-[2-methylpiperidin-1-yl]propylamino)-2-oxoethyl]-1,2-  
15 dimethylimidazolium chloride;  
3-(2-veratrylamino-2-oxoethyl)-1,2-dimethylimidazolium chloride;  
3-[2-(thiazolidin-3-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-(1-adamantanamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-(2-adamantanamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
20 3-[2-(2-indanylamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-(2'-[3"-chlorobenzoyl]-5-chloroanilino)-2-oxoethyl]-1,2-  
dimethylimidazolium chloride;  
3-[2-(4-ethoxycarbonylthiazol-2-yl)amino-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
25 3-(cyclohexylamino-2-oxoethyl)-2,4,5-trimethylthiazolium chloride;  
3-[2-(2-chloroanilino)-2-oxoethyl]-1,2-dimethylimidazolium bromide;  
3-[2-(2-chloroanilino)-2-oxoethyl]-2,4,5-trimethylthiazolium bromide;  
3-[2-(3,4-dimethoxyphenethylamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
30 3-[2-(2,4-dichloroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[2-(2,6-dichloroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
3-[(2-pyrrolidin-1-yl)-2-oxoethyl]-1,2,4,5-tetramethylimidazolium chloride;

3-[2-(4-[pyrrolidin-1-yl]piperidin-1-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

3-[2-(4-[piperidin-1-yl]piperidin-1-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

5       3-[2-(2,6-difluoroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
       3-(2-cyclobutylamino-2-oxoethyl)-1,2-dimethylimidazolium chloride;  
       3-[2-(3,5-difluoroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
       3-[2-(2-fluoroanilino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
       3-[2-(1R,2R,3R,5S-isopinocampheylamino)-2-oxoethyl]-1,2-

10      dimethylimidazolium chloride;  
       3-[2-(1,3,3-trimethyl-6-azabicyclo[3.2.1]octanyl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
       3-[2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-oxoethyl]-1,2-dimethylimidazolium chloride;

15      3-[2-(1,2,3,4-tetrahydro-1-naphthylamino)-2-oxoethyl]-1,2-dimethylimidazolium chloride;  
       1-(4-methoxyphenyl)-3-aminoimidazolium mesitylenesulfonate;  
       1-benzyl-3-aminoimidazolium mesitylenesulfonate;  
       1-vinyl-3-aminoimidazolium mesitylenesulfonate;

20      1-methyl-3-aminoimidazolium mesitylenesulfonate;  
       1-(4-methoxycarbonylphenyl)-3-aminoimidazolium mesitylenesulfonate;  
       3-(2-phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium;  
       S(-) 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride;  
       R(-) 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride;

25      3-[2-(2-Hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;  
       3-[2-(3-Hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;  
       3-[2-(4-Hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;  
       3-(2-phenyl-2-oxoethyl)-4-methyl-5-(hydroxymethyl)-thiazolium chloride;  
       3-[2-(2,4-dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

30      3-[2-(3,5-dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;  
       3-[2-(2,5-dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;  
       3-[2-(3, 4-dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride;  
       3-[2-(2', 3'-dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium;

thiamine hydrochloride;

(1-ethyl-hexanoate)-3-[2-(4-chlorophenyl)-2-oxoethyl]imidazolium bromide;

3-[2-[6-[1,2,3,4-tetrahydro-1,1,4, 4-tetramethyl-naphthalyl]]-2-oxoethyl]thiazolium bromide;

5 3-[2-(3,5-dichloroanilino)-2-oxoethyl]thiazolium bromide;

3-[2-(4-biphenyl)-2-oxoethyl]thiazolium bromide;

Cocarboxylase (diphosphate ester of thiamine HCl);

monophosphate ester of thiamine HCl;

3-[2-(9H-fluoren-2-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

10 3-[2-{6-(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-naphthalyl)}-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-{5-(3-phenylisoxazolyl)}-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(4-biphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(3,5-dichloroanilino)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

15 3-[2-{6-[1,2,3,4-tetrahydro-1,1,4, 4-tetramethyl-naphthalyl]}-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-[2-(3-phenylisoxazol-5-yl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-[2-(4-biphenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

20 3-[2-(3,5-dichloroanilino)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-{{2-(3-methoxybenzoyl)amino]benzyl}-4,5-dimethylthiazolium bromide;

3-[2-(2-amino-5-carboethoxymethylene-thiazolyl)-2-oxoethyl]-4,5-dimethylthiazolium choride;

25 3-[2-(morpholin-4-yl-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(2,6-dimethylmorpholin-4-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(piperidin-1-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(fur-2-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-[6-(2-oxo-1,2,3,4-tetrahydroquinolinyl)]-2-oxoethyl]-4,5-

30 dimethylthiazolium bromide;

3-[2-(pyrrolidin-1-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(4-carboxyanilino)-2-oxoethyl]-4,5-dimethylthiazolium chloride;

3-[2-(2-{3-methylbenzo[b]thienyl})-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(4-phenylpiperazin-1-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(4-fluorophenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

5 3-[2-(4-methoxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(4-trifluoromethyl)-2-oxoethyl]-4,5-dimethyl-thiazolium bromide;

3-[2-(2,4-difluorophenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride;

3-[2-tert-butyl-2-oxoethyl]-4,5-dimethylthiazolium chloride;

10 3-[2-(2,4-dichlorophenyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride;

3-[2-(4-Diethylaminophenyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride;

3-(2-methyl-2-oxoethyl)-4,5-dimethylthiazolium chloride;

3-[2-(2,6-dichlorophenyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride;

3-(2-phenyl-2-oxoethyl)-4-phenylthiazolium chloride;

15 3-[2-(2,4-dichlorophenyl)-2-oxoethyl]-4-phenylthiazolium chloride;

3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]-4-phenylthiazolium bromide;

3-(2-methyl-2-oxoethyl)-4-methyl-5-(hydroxyethyl) thiazolium chloride;

3-[2-(2,4-dichlorophenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium;

3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium

20 chloride;

3-(1-methyl-2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride;

3-(phenylthiomethyl)-4,5-dimethylthiazolium chloride;

3-[2-(thien-2-yl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-(2-thien-2-yl)-2-oxoethyl]-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

25 3-[2-phenyl-2-oxoethyl]-4,5-cyclohexenyl-thiazolium bromide;

3-[2-(2,4-dichlorophenyl)-2-oxoethyl]-4,5-cyclohexeno-thiazolium chloride;

3-(2-phenyl-2-oxoethyl)-4,5-cyclopenteno-thiazolium bromide;

3-[2-(2,4-dichlorophenyl)-2-oxoethyl]-4,5-cyclopenteno-thiazolium chloride;

3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]-4,5-cyclopenteno-thiazolium bromide;

30 3-[2-(2,4,6-trimethylphenyl)-2-oxoethyl]-4,5-cyclopenteno-thiazolium bromide;

3-(2-cyanomethyl)-4,5-cyclohexeno-thiazolium bromide;

3-(2-cyanomethyl)-4,5-cyclopenteno-thiazolium bromide;

3-(2-cyanomethyl)-4,5-dimethyl-thiazolium bromide;

3-(2-methyl-2-oxoethyl)-4,5-cyclopenteno-thiazolium chloride;

3-(2-cyanomethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium bromide;

3-(2-phenyl-2-oxoethyl)-4-methyl-5-(hydroxyethylsuccinyl)thiazolium chloride;

3-[2-(thien-2-yl)-2-oxoethyl]-2,4,5-trimethylthiazolium bromide;

5 3-amino-4-methyl-5-(2-hydroxyethyl)-thiazolium bromide;

3-(2-phenyl-2-oxoethyl)-2,4,5-trimethylthiazolium chloride;

3-amino-2,4,5-trimethylthiazolium mesitylenesulfonate;

3-[2-(4-{2-methoxyphenyl}piperazin-1-yl)-2-oxoethyl]-4,5-dimethylthiazolium chloride;

10 3-[2-hydroxy-2-oxoethyl]-4,5-dimethylthiazolium chloride;

3-(2-phenyl-2-oxoethyl)-2-aminothiazolium chloride;

3-[2-(thiomorpholin-4-yl)-2-oxoethyl]-5-hydroxyethyl-4-methylthiazolium chloride;

15 3-[2-(4-trifluoromethylphenyl)-2-oxoethyl]-2,4,5-trimethylthiazolium bromide;

3-[2-phenyl-2-oxoethyl]-2-isobutylthiazolium chloride;

3-[2-(thiomorpholin-4-yl)-2-oxoethyl]-2,4,5 trimethylthiazolium chloride;

3-(2-amino-2-oxoethyl)-2-methylbenzothiazolium chloride;

3-[2-(4-acetanilino)-2-oxoethyl]-2,4,5-trimethylthiazolium chloride;

3-[2-(4-carboethoxyanilino)-2-oxoethyl]-2,4,5-trimethylthiazolium bromide;

20 3-[2-(2,6-diisopropylanilino)-2-oxoethyl]-2,4,5-trimethylthiazolium bromide;

3-[(4-bromoanilino)-2-oxoethyl]-2,4,5-trimethylthiazolium chloride;

3-[2-(2-naphthyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-([3-phenylisoxazol-5-yl])-2-oxoethyl]thiazolium bromide;

3-methyl-4,5-dimethylthiazolium chloride;

25 3-ethyl-4,5-dimethylthiazolium bromide;

3-[2-(4'-acetoxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide;

3-[2-phenyl-2-oxoethyl]-4-methyl-5-(ethoxycarbonyl)thiazolium chloride;

3-[2-(4-diethylaminophenyl)-2-oxoethyl]thiazolium chloride;

1-methyl-3-(2-cyanomethyl)imidazolium bromide ;

30 3-(2-cyanomethyl)-4,5-dimethylthiazolium bromide;

3-(2-cyanomethyl)-4,5-cyclopentenothiazolium bromide;

3-(2-cyanomethyl)-4,5-cyclohexenothiazolium bromide;

1-methyl-3-(2-cyanomethyl)imidazolium bromide;

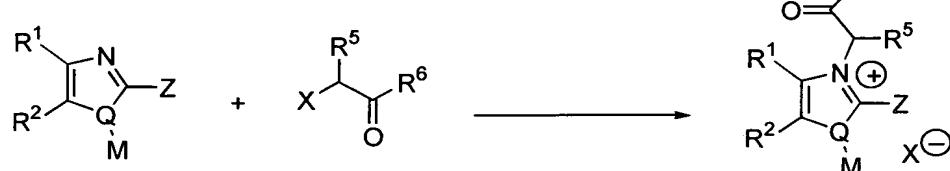
1-vinyl-3-(2-cyanomethyl)imidazolium chloride;  
 1-allyl-3-(2-cyanomethyl)imidazolium chloride;  
 1-(4-acetylphenyl)-3-(2-cyanomethyl)imidazolium chloride;  
 1-phenyl-3-(2-cyanomethyl)imidazolium chloride;  
 5 1-(4-methoxyphenyl)-3-(2-cyanomethyl)imidazolium chloride;  
 1-(4-methoxycarbonylphenyl)-3-(2-cyanomethyl)imidazolium chloride;  
 3-(2-cyanomethyl)-1-methylbenzimidazolium chloride;  
 1,5-dicyclohexyl-3-(2-cyanomethyl)imidazolium bromide;

10 as well as other biologically or pharmaceutically acceptable salts thereof.

Compounds of the general formula I wherein the R<sup>1</sup>, R<sup>2</sup>, X, Y, and Z are defined as above can be prepared by the methods of US 5,656,261; 5,853,703; and 6,007,865; or as described below. Moreover, certain of the compounds are conveniently prepared by chemical syntheses that are well-known in the art. In addition, certain of the compounds 15 are well-known and readily available from chemical supply houses or can be prepared by synthetic methods specifically published therefor. The chemical reagents shown in the schemes below provide nonlimiting examples of means well known in the art to carry out the reaction steps shown.

Compounds of the invention wherein Y is CH(R<sup>5</sup>)-C(O)-R<sup>7</sup> can be prepared 20 according to the synthetic route depicted in **Scheme 1** (wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>5</sup>, R<sup>7</sup>, M, Q, and Z are as described above, and X is a halide). An acetyl derivative with a suitable a  $\alpha$  leaving group, for example, an  $\alpha$ -halo acetyl derivative, can be used to alkylate a suitably substituted thiazole, oxazole, or imidazole. The alkylation reaction may be conducted at elevated temperatures in a suitable solvent, for example, acetonitrile or ethanol, or 25 without solvent.

**Scheme 1**



Compounds of the invention wherein  $R^6$  is a group of the formula  $-CH(OH)Rs$  may be prepared as shown in **Schemes 2** and **3** (see below). In the nonlimiting exemplary synthetic schemes below, some product compounds are shown as specific optical isomers and others are shown as racemic compounds. One skilled in the art will

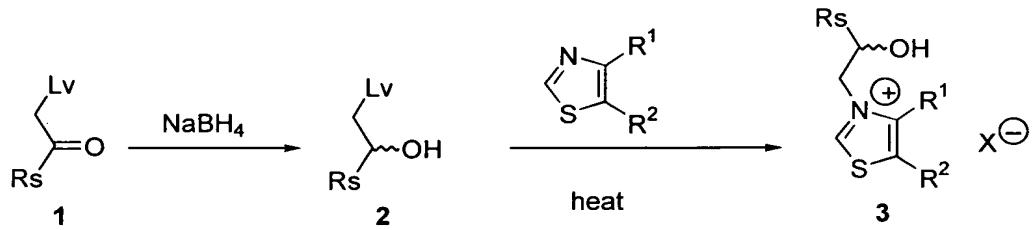
5 appreciate that appropriate reaction conditions and reagents, that are well known in the art, can be used to customize the degree of reaction stereoselectivity. Thus, isolated stereoisomers are within the scope of compounds of the invention. For example, compound **2** can be obtained as a racemic mixture from compound **1** or as an S (compound **2a**) or R stereoisomer depending on the reducing agent employed.

10 Substitution of comparable reagents to achieve different stereoselectivity, even when not shown explicitly by the scheme, is well known in the art at the time of filing. Moreover, synthetic processes and stereoselective purifications, such as chromatography on stereoselective media can be used to achieve 90%, 95%, 98%, 99% or better isomeric purity, such that compositions substantially free of the non-desired isomer can be

15 prepared.

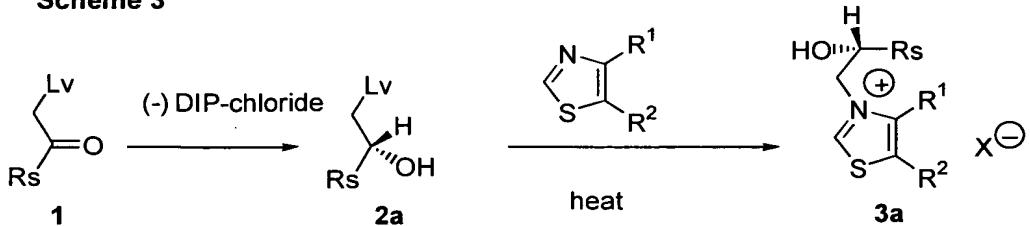
A synthetic scheme for making compounds of the formula I wherein Y is  $CH_2CH(OH)Rs$  is shown in **Scheme 2**. A hydroxyl is incorporated into a nucleophile used to derivatize a thiazole compound, as follows:

**Scheme 2**



20 where Lv is a leaving group such as chloro. In a related synthesis, Compound **1** is reduced with a stereoselective reducing agent such as (-)-DIP-chloride [(-)-B-chlorodiisopinocampheylborane] or (+)-DIP-chloride [(+)-B-chlorodiisopinocampheylborane]. For example:

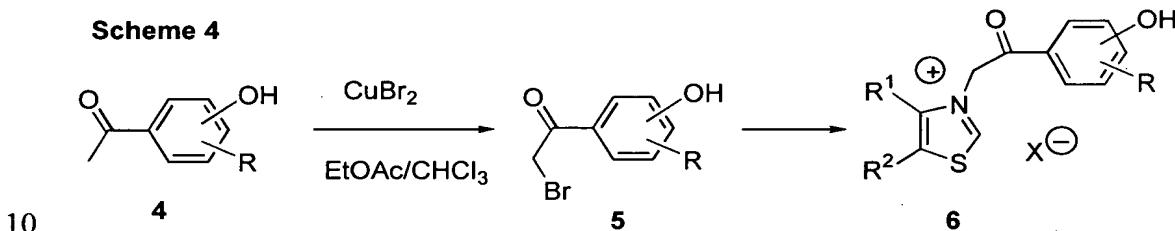
### Scheme 3



Substitution of (+) DIP-chloride results predominately in the mirror image to compound **3a**.

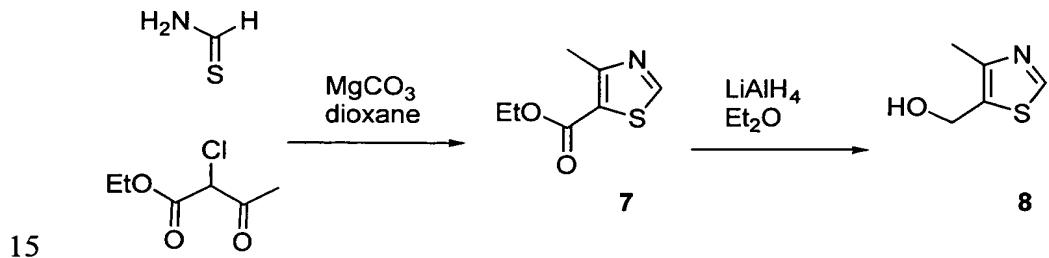
**Scheme 4** exemplifies methods of preparing compounds of the formula I wherein Y is a group of the formula -CH<sub>2</sub>R<sup>6</sup> wherein R<sup>6</sup> is a substituted or unsubstituted benzoyl moiety. In this particular preparation, acetophenones substituted in the phenyl moiety with hydroxy groups are derivatized to add a leaving group to the alpha methyl group, and the resulting intermediate is then used to alkylate thiazoles, as exemplified below:

**Scheme 4**



In another synthesis, the preparation of compounds of the formula I wherein  $R^2$  is  $-CH_2OH$  are exemplified. Formamide is first converted to thioformamide by reaction with phosphorus pentasulfide. Thioformamide is reacted with ethyl 2-chloroacetoacetate in dry dioxane as follows:

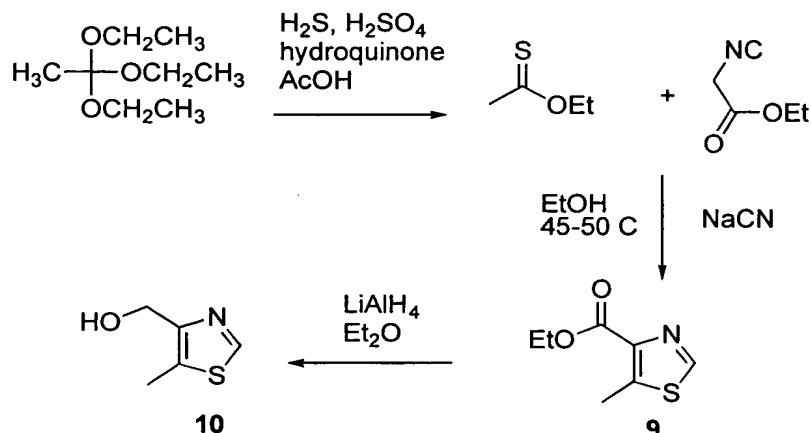
### Scheme 5



Compound **8** can then be reacted with a suitable alkylating agent to make a compound of the invention.

Where R<sup>1</sup> is -CH<sub>2</sub>OH and R<sup>2</sup> is -CH<sub>3</sub> in Formula I, the route shown in **Scheme 6** can be used. The preparation of a thiazole analog containing a 4-hydroxymethyl group, for example, is shown below:

### Scheme 6

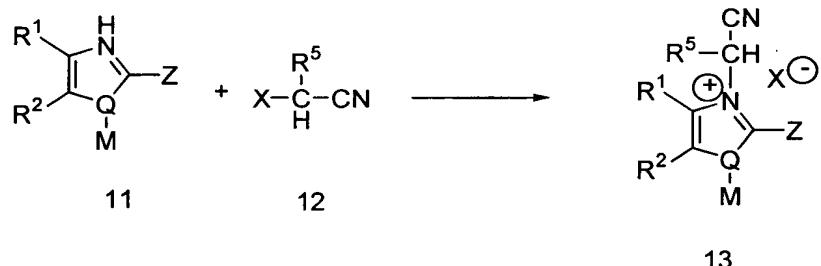


Compound **10** can then be alkylated with a suitable alkylating agent to make a compound of the invention.

Note that reaction conditions indicated in the various reaction schemes are exemplary: such conditions as solvent and temperature are subject to modification within ordinary skill.

A useful synthetic route for the preparation of compounds of formula I wherein Y is  $-\text{CH}(\text{R}^5)\text{CN}$  is shown in **Scheme 7**.

**Scheme 7**

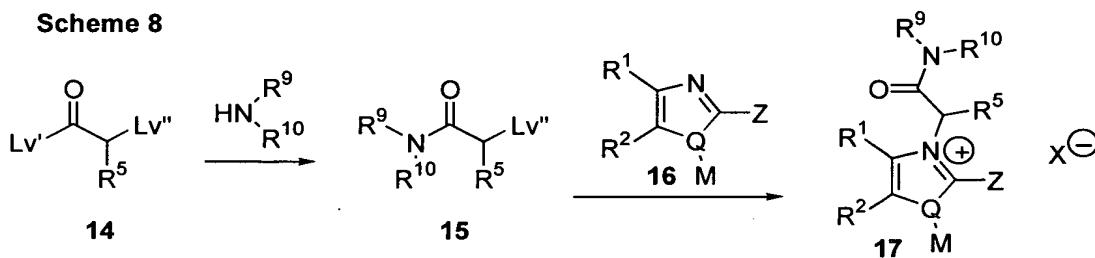


wherein M, Q, R<sup>1</sup>, R<sup>2</sup>, R<sup>5</sup>, Y and Z are as described in the text above, and X is a halide, 15 mesitylenesulfonate or other biologically acceptable anion. In **Scheme 7**, the appropriately substituted imidazole, oxazole, or thiazole of formula **11** is contacted with a (e.g.) halo substituted acetonitrile of formula **12** to produce compounds of the formula **13**. The reaction can be performed without any added solvent, or an anhydrous solvent can be utilized as the solvent medium. When a solvent is used, acetonitrile is a typical

solvent for this reaction. Reaction times vary according to particular reactants and conditions, but are usually in the range of a few minutes to 48 hours at a temperature of 25-130°C.

Compounds of the formula 17 (below), wherein Y contains a carboxamido moiety, can be synthesized according to method depicted in **Scheme 8**. An appropriately substituted amine can be condensed with an activated acetyl analog (for example, an acid chloride or acid anhydride), containing an additional leaving group alpha to the carbonyl group, to provide the carboxamide 15. Compound 15 can then be used to alkylate the heterocycle 16 to yield a compound of the invention 17.

10

**Scheme 8**

Other alkylation conditions can also be used. For example, thiazoles and imidazoles can be alkylated at the 1-position or the 2-position by vapor phase alkylation over an appropriate solid catalyst, using the corresponding alcohol as the alkyl source.

See, Ono et al., in *Catalysis by Microporous Materials*, Studies in Surface Science and Catalysis, Vol. 94, Beyer et al., Eds., 1995, polypeptide.697-704. Appropriate catalysts include zeolite H-Y, zeolite H-ZSM-5 and H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> supported on silica. Reaction conditions typically include high temperatures, such as 260 and 300 °C.

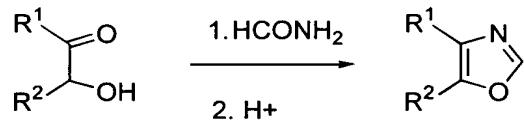
In addition, N-aryl substituted thiazoliums, oxazoliums and imidazoliums can also be prepared. For example, fluoro phenyl compounds such as 4-fluorobenzoic acid methyl ester can be used to substitute the N<sup>1</sup> nitrogen of imidazole to make methyl-4-(1H-imidazol-1-yl)benzoate. See, Morgan et al., *J. Med. Chem.* 33: 1091-1097, 1990. These aryl substituted imidazoliums can then be reacted with an alkylating agent, for example, an α-haloacetophenone analog, to prepare a compound of the invention. Also, the amine functions of imidazoles or amine-substituted thiazoles can be acylated by dehydration or other methods known in the art.

3-Aminothiazoliums, 3-aminooxazoliums, and 1-alkyl-3-aminoimidazoliums can be prepared by reaction with O-mesitylene sulfonylhydroxylamine in methylene chloride. The product mesitylenesulfonate salts can be converted to their chloride salts through ion exchange with strongly basic anion exchange resins.

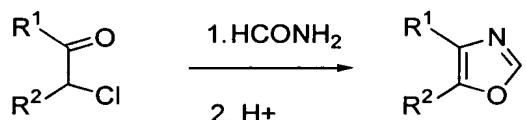
5 Substituted oxazole intermediate that are suitable intermediates for the alkylation reactions, such as those shown in **Schemes 1** and **7**, can be prepared by methods known in the art. For instance, 2-unsubstituted oxazoles can be formed by condensation of formamide with either  $\alpha$ -hydroxy or  $\alpha$ -haloketones intermediates (H. Bredereck, R. Gommpper, H. G. v. Shuh and G. Theilig, in *Newer Methods of Preparative Organic Chemistry*, Vol. III, ed. W. Foerst, Academic press, New York, 1964, p. 241). The intermediates can cyclize under acid conditions to form the oxazole ring (**Scheme 9**). In addition, 2,4-disubstituted oxazoles can be prepared from  $\alpha$ -haloketones and amides at higher temperatures using the same method.

10

**Scheme 9**



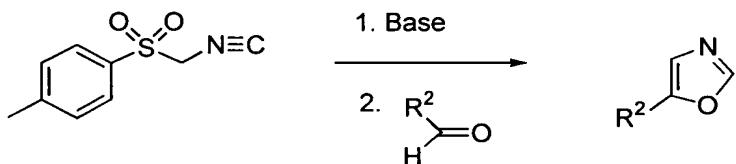
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Oxazoles can be prepared by cyclization reactions of isonitriles (van Leusen, A. M. *Lect. Heterocycl. Chem.* **1980**, 5, S111; Walborsky, H. M.; Periasamy, M. P. in *The Chemistry of Functional Groups, suppl. C*, Patai, S., Rappoport, Z., Eds, Wiley-Interscience, 1983, p. 835; Hoppe, D. *Angew. Chem. Int. Edn. Engl.*, **1974**, 13, 789; Schollkopf, U. *Angew. Chem. Int. Ed. Engl.*, **1977**, 16, 339). For example, as shown below in **Scheme 10**, the tosylmethyl isocyanide can be deprotonated by a base and reacted with a suitable electrophile (e.g. an aldehyde). The intermediate can cyclize and aromatize to provide the desired oxazole intermediate. The intermediate can then be N-alkylated by the above-described methods to furnish a compound of the invention. Other methods for preparing oxazole intermediates include 1,5-dipolar cyclization of acylated

nitrile ylides (Taylor E. C.; Turchi, I. J. *Chem. Rev.*, **1979**, *79*, 181; Huisgen, R. *Angew. Chem. Int. Edn. Engl.* **1980**, *19*, 947).

Scheme 10

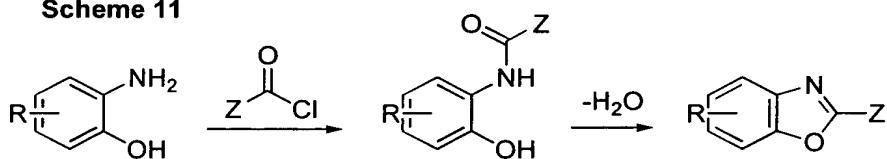


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Benzoxazole intermediates substituted at the 2 position can be prepared from 2-aminophenols by acylation with, for example, with an acid chloride and cyclization (Scheme 11). The intermediate can then be N-alkylated by the above-described methods to furnish a compound of the invention.

10

Scheme 11



To treat the indications of the invention, an effective amount of a pharmaceutical compound will be recognized by clinicians but includes an amount effective to treat, 15 reduce, ameliorate, eliminate or prevent one or more symptoms of the disease sought to be treated or the condition sought to be avoided or treated, or to otherwise produce a clinically recognizable change in the pathology of the disease or condition.

Pharmaceutical compositions can be prepared to allow a therapeutically effective quantity of the compound of the present invention, and can include a pharmaceutically acceptable carrier, selected from known materials utilized for this purpose. *See, e.g.*, Remington, *The Science and Practice of Pharmacy*, 1995; *Handbook of Pharmaceutical Excipients*, 3<sup>rd</sup> Edition, 1999. Such compositions can be prepared in a variety of forms, depending on the method of administration, such as sublingual, rectal, nasal, vaginal, topical (including the use of a patch or other transdermal delivery device), by pulmonary 25 route by use of an aerosol, or parenteral, including, for example, intramuscular, subcutaneous, intraperitoneal, intraarterial, intravenous or intrathecal..

In addition to the subject compound, the compositions of this invention can contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances that are suitable for administration to an animal, including a 5 mammal or human. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, such that there is no interaction that would substantially reduce the pharmaceutical efficacy of the composition under ordinary use. Preferably when liquid dose forms are used, the compounds of the invention are soluble in the components of 10 the composition. Pharmaceutically-acceptable carriers should, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, 15 such as corn starch and-potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, 20 mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the Tween<sup>TM</sup> brand emulsifiers; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions. The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically 25 determined by the way the compound is to be administered. If the subject compound is to be injected, the preferred pharmaceutically-acceptable carrier is sterile, physiological saline, with a blood-compatible suspending agent, the pH of which has been adjusted to about 7.4.

If the preferred mode of administering the subject compound is perorally, the 30 preferred unit dosage form is therefore tablets, capsules, lozenges, chewable tablets, and the like. Such unit dosage forms comprise a safe and effective amount of the subject compound, which is preferably from about 0.7 or 3.5 mg to about 280 mg/ 70 kg, more preferably from about 0.5 or 10 mg to about 210 mg/ 70 kg. The pharmaceutically-

acceptable carrier suitable for the preparation of unit dosage forms for peroral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and 5 sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder-mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable 10 tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this invention, and can be readily made by a person skilled in the art.

Peroral compositions also include liquid solutions, emulsions, suspensions, and 15 the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Such liquid oral compositions preferably comprise from about 0.012% to about 0.933% of the subject compound, more preferably from about 0.033% to about 0.7%. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene 20 glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, cellulose (e.g. Avicel<sup>TM</sup>, RC-591), tragacanth and sodium alginate; typical wetting agents include lecithin and polyethylene oxide sorbitan (e.g. polysorbate 80). Typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more 25 components such as sweeteners, flavoring agents and colorants disclosed above.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual and buccal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and 30 hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

Compositions can also be used to deliver the compound to the site where activity is desired; such as eye drops, gels and creams for ocular disorders.

Compositions of this invention include solutions or emulsions, preferably aqueous solutions or emulsions comprising a safe and effective amount of a subject compound intended for topical intranasal administration. Such compositions preferably comprise from about 0.01% to about 10.0% w/v of a subject compound, more preferably from about 0.1% to about 2.0%. Similar compositions are preferred for systemic delivery of subject compounds by the intranasal route. Compositions intended to deliver the compound systemically by intranasal dosing preferably comprise similar amounts of a subject compound as are determined to be safe and effective by peroral or parenteral administration. Such compositions used for intranasal dosing also typically include safe and effective amounts of preservatives, such as benzalkonium chloride and thimerosal and the like; chelating agents, such as edetate sodium and others; buffers such as phosphate, citrate and acetate; tonicity agents such as sodium chloride, potassium chloride, glycerin, mannitol and others; antioxidants such as ascorbic acid, acetylcystine, sodium metabisulfite and others; aromatic agents; viscosity adjustors, such as polymers, including cellulose and derivatives thereof; and polyvinyl alcohol and acids and bases to adjust the pH of these aqueous compositions as needed. The compositions may also comprise local anesthetics or other actives. These compositions can be used as sprays, mists, drops, and the like.

Other preferred compositions of this invention include aqueous solutions, suspensions, and dry powders comprising a safe and effective amount of a subject compound intended for atomization and inhalation administration. Such compositions are typically contained in a container with attached atomizing means. Such compositions also typically include propellants such as chlorofluorocarbons 12/11 and 12/114, and more environmentally friendly fluorocarbons, or other nontoxic volatiles; solvents such as water, glycerol and ethanol, including cosolvents as needed to solvate or suspend the active agent; stabilizers such as ascorbic acid, sodium metabisulfite; preservatives such as cetylpyridinium chloride and benzalkonium chloride; tonicity adjustors such as sodium chloride; buffers; and flavoring agents such as sodium saccharin. Such compositions are useful for treating respiratory disorders, such as asthma and the like.

Other preferred compositions of this invention include aqueous solutions comprising a safe and effective amount of a subject compound intended for topical ocular administration. Such compositions preferably comprise from about 0.01% to about 0.8% w/v of a subject compound, more preferably from about 0.05% to about

0.3%. Such compositions also typically include one or more of preservatives, such as benzalkonium chloride or thimerosal; vehicles, such as poloxamers, modified celluloses, povidone and purified water; tonicity adjustors, such as sodium chloride, mannitol and glycerin; buffers such as acetate, citrate, phosphate and borate; antioxidants such as 5 sodium metabisulfite, butylated hydroxy toluene and acetyl cysteine; acids and bases can be used to adjust the pH of these formulations as needed.

Other preferred compositions of this invention useful for peroral administration include solids, such as tablets and capsules, and liquids, such as solutions, suspensions and emulsions (preferably in soft gelatin capsules), comprising a safe and effective 10 amount of a subject compound. Such compositions can be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl 15 cellulose, Eudragit<sup>TM</sup> coatings, waxes and shellac.

The compounds of the invention are administered by ocular, oral, parenteral, including, for example, using formulations suitable as eye drops. For ocular administration, ointments or droppable liquids may be delivered by ocular delivery systems known to the art such as applicators or eye droppers. Such compositions can 20 include mucomimetics such as hyaluronic acid, chondroitin sulfate, hydroxypropyl methylcellulose or polyvinyl alcohol, preservatives such as sorbic acid, EDTA or benzylchromium chloride, and the usual quantities of diluents and/or carriers. See, Remington's Pharmaceutical Sciences, 16th Ed., Mack Publishing, Easton, PA, 1980, as well as later editions, for information on pharmaceutical compounding.

25 Numerous additional administration vehicles will be apparent to those of ordinary skill in the art, including without limitation slow release formulations, liposomal formulations and polymeric matrices.

In another preferred embodiment, the pharmaceutically effective amount is approximately 0.1 or 0.5 to 4 mg/kg body weight daily. Still more preferably, the 30 pharmaceutically effective amount is approximately 1 mg/kg body weight daily. In a preferred embodiment, the amount is administered in once daily doses, each dose being approximately 1 mg/kg body weight.

The activity of the compounds of the invention in breaking, reversing or inhibiting the formation of AGE's or AGE-mediated crosslinks can be assayed by any of the methods described in US Patent 5,853,703.

The following examples further illustrate the present invention, but of course, 5 should not be construed as in any way limiting its scope.

**Example**

Rats received a daily intraperitoneal dose of 10 mg/kg 3-[2-phenyl-2-oxoethyl]-4,5-dimethyl-thiazolium salt (compound A) (n=14) or placebo (n=15) for 30 days. The 10 animals then underwent a thoracotomy and the left anterior descending coronary artery ligated. The chest was then closed and the animals allowed to recover for 14 days while continuing to be treated with compound A or placebo. The animals were then sacrificed and the hearts removed for histological examination. The weight of the infarcted tissue was  $0.16 \pm 0.04$  g for the placebo treated animals compared to  $0.11 \pm 0.05$  g for the compound 15 A treated animals ( $p=0.04$ ). The thickness of the ventricular wall in the infarcted zone was also reduced in the compound A treated animals compared to placebo ( $2.72 \pm 0.13$  mm vs.  $2.56 \pm 0.22$  mm,  $p=0.09$ ).

**EXAMPLE 1. 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride: 2-Chloro-1-phenylethanol:**  
2-Chloroacetophenone (5.0 g, 32 mmol) was dissolved in methanol (25 mL) and cooled to 0°C. Sodium borohydride (1.2 g, 32 mmol) was added and stirred at 0°C for 30 minutes. The reaction mixture was neutralized by adding conc. HCl to pH 7.0 and evaporated to dryness. The residue was dissolved in ethanol (30 mL) and filtered, 25 washed with ethanol. The ethanol was evaporated to dryness. The residue was dissolved in methylene chloride (20 mL) and dried over sodium sulfate. The methylene chloride solution was filtered and evaporated to give the desired product as an oil; yield 4.84 g (5.6%).

**3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride:**

30 The neat mixture of 2-chloro-1-phenylethanol (2.34 g, 14.9 mmol) and 4,5-dimethylthiazole (1.69 g, 14.9 mmol) were heated with stirring at 135°C for 28 hrs. It

was cooled to room temperature and water (30 mL) was added to the reaction mixture with stirring, and then was extracted with ether (30 mL). The water layer was treated with activated carbon and evaporated to dryness. It was crystallized from a mixture of acetonitrile and ether to give a racemic product as prisms; 0.39 g (9.7%); mp. 201-  
5 203°C.

**EXAMPLE 2. S 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride:**

**S (-) 2-chloro-l-phenylethanol.**

2-Chloroacetophenone (3 g., 19.4 mmol) was treated with (-) DIP-chloride (6.7 g., 20.9 mmol) in anhydrous THF (20 mL) at dry-ice bath temperature and left overnight. The 10 temperature was raised to room temperature and THF was removed in vacuo. The residue was dissolved in ether (100 mL). The diethanolamine (4.58 g., 42.6 mmol) was added and the mixture stirred at room temperature for 5 hrs. The separated solid was filtered and the filtered cake was washed with hexane (40 mL) and ether (30 mL). The combined filtrates were evaporated to dryness to give 6.36 g of crude product. This was 15 purified by silica gel column chromatography using 1 % ether and petroleum ether 1.71 g (56 %) of the desired product was obtained as an oil.

**S 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride.**

The neat mixture of S (-) 2-chloro-l-phenylethanol (2.78 g., 17.8 mmol) and 4,5-dimethylthiazole (2 g., 17.7 mmol) were heated with stirring at 135°C for 25 hrs. It was 20 cooled to room temperature and water (30 mL) was added to the reaction mixture with stirring. The solution was extracted with ether (30 mL). The ether extract was again extracted with water (30 mL). The combined water layer was evaporated to dryness and the residue was crystallized with a mixture of acetonitrile and methyl tert-butyl ether. Yield: 0.63 g. (7.7 %); mp. 189-190°C;  $[\alpha]_D^{25} -51.765$  ( Water, c = 1.7732).

25 **EXAMPLE 3. R(+) 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride:**

**R(+) 2-chloro-l-phenylethanol.**

2-Chloroacetophenone (6.25 g., 40.4 mmol) was treated with (+) DIP-chloride (18 g., 56.1 mmol) in anhydrous THF (40 mL) at dry-ice bath temperature and left overnight.

The temperature was raised to room temperature and THF was removed in vacuo. The residue was dissolved in ether (210 mL). The diethanolamine (9 g., 85.6 mmol) was added and the mixture stirred at room temperature for 5 hrs. The separated solid was filtered and the filtered cake was washed with ether (150 mL). The combined filtrates 5 were evaporated to dryness to give 15.53 g. of crude product. This was purified by silica gel column chromatography using 1 % ether and petroleum ether 4.32 g (68 %) of the desired product as an oil.

**R (+) 3-(2-Phenyl-2-hydroxyethyl)-4,5-dimethylthiazolium chloride.**

The neat mixture of R (+) 2-chloro-1-phenylethanol (4.32 g., 27.6 mmol) and 4,5-10 dimethylthiazole (3.12 g, 27.6 mmol) were heated with stirring at 135°C for 25 hrs. It was cooled to room temperature and water (30 mL) was added to the reaction mixture with stirring. The solution was extracted with ether (30 mL). The ether extract was again extracted with water (30 mL). The combined water layer was evaporated to dryness and the residue was crystallized with a mixture of acetonitrile and methyl tert-15 butyl ether. Yield: 0.44 g. (5.4 %); mp. 187-189°C;  $[\alpha]_D^{25} +52.009$  (Water, c = 1.7824).

**EXAMPLE 4. 3-[2-(2', 3' or 4'-monohydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide.**

**2-Bromo-4'-hydroxyacetophenone.**

20 Copper (II) bromide (6 g, 26.9 mmol) was suspended in ethyl acetate (50 mL) and 4'-hydroxyacetophenone (2 g, 14.7 mmol) dissolved in chloroform (20 mL) was added to the suspension. The reaction mixture was refluxed for 8 hrs. and filtered hot through celite pad. The filtrate was evaporated to dryness to give the desired crude brown colored compound (mp=115-118°C; yield: 3.03 g, 96%). The NMR spectrum and TLC 25 [silica gel, Hexanes:EtOAc (1:1, v/v)] was in agreement with the desired product. It was used as such in the next step of the reaction without further purification.

This method was used to prepare:

(i) 2-Bromo-2'-hydroxyacetophenone from 2'-hydroxyacetophenone and copper (II) bromide. Yield: 3.30 g. (95%; oil).

(ii) 2-Bromo-3'-hydroxyacetophenone from 3'-hydroxyacetophenone and copper (II) bromide. Yield: 3.20 g. (92%; oil).

**3-[2-(4-Hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide.**

The neat mixture of 2-bromo-4'-hydroxyacetophenone (3 g, 15 mmol) and 4,5-dimethylthiazole (1.71 g, 15 mmol) was heated at 110°C for 3 hrs. It was dissolved in acetonitrile (15 mL) and cooled to room temperature. Tert-butyl methyl ether (5 mL) was added and the reaction mixture kept at room temperature overnight. The product crystallized was filtered, washed well with a mixture of acetonitrile and tert-butyl methyl ether (1:1, v/v) and dried. It was recrystallized from a mixture of acetonitrile, ethyl alcohol and tert-butyl methyl ether. Yield: 3.18 g (64%); mp. 245-247°C (dec.).

This method was used to prepare:

(i) 3-[2-(2-Hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide from 2-bromo-2'-hydroxyacetophenone and 4,5-dimethylthiazole. Yield: 2.05 g. (38%), mp = 208-209°C.

15 (ii) 3-[2-(3-Hydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide from 2-bromo-3'-hydroxyacetophenone and 4,5-dimethylthiazole. Yield: 1.52 g. (47%), mp = 235-237°C.

**EXAMPLE 5. 3-(2-Phenyl-2-oxoethyl)-4-methyl-5-(hydroxymethyl)thiazolium chloride**

**Thioformamide.**

To formamide (20 g, 443 mmol) dissolved in anhydrous THF (100 mL) was added phosphorous pentasulfide ( $P_2S_5$ ) (20 g, 45 mmol) while maintaining the temperature at 30-35°C. The mixture was stirred overnight at room temperature, filtered and stripped of THF. The crude product was suspended in ethyl acetate (40 mL) and cooled at -78°C overnight, filtered and dried in vacuo at room temperature to give thioformamide (10.6 g, 39%). *See Rynbrandt, R.H., Nishizawa, E.E., Balogoyen, D.P., Mezdoza, A.K., Annis, K.A.; J. Med. Chem. 1981, 24, 1507-1510.*

**4-Methyl-5-(ethoxycarbonyl)thiazole.**

Thioformamide (7.5 g, 122.72 mmol), ethyl 2-chloroacetoacetate (16.4 g, 99.52 mmol) and magnesium carbonate (20 g, 237.22 mmol) were taken dioxane (100 mL) and heated at 110°C for 4 hrs. The reaction mixture was cooled to room temperature and 5 filtered to remove magnesium carbonate. The solvent was evaporated to dryness and the residue was taken in ether (200 mL) and washed successively with 0.5 M NaOH solution (200mL x 2) and saturated brine solution (100 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. It was filtered and evaporated to give 4-methyl-5-(ethoxycarbonyl)thiazole as an oil which was purified by silica gel column chromatography using hexanes:EtOAc (8:2, v/v) as a 10 eluent; yield: 3.28 g (17%).

**4-Methyl-5-(hydroxymethyl)thiazole.**

A 250-mL, three necked round-bottomed flask fitted with a 100-mL dropping funnel, a nitrogen-inlet tube, and a reflux condenser was added lithium aluminum hydride (1 g, 15 26.35 mmol) and anhydrous ether (50mL). To the dropping funnel was added 4-methyl-5-(ethoxycarbonyl)-thiazole (3 g, 17.3 mmol) and anhydrous ether (25 mL). While the suspension of lithium aluminum hydride was gently stirred under a nitrogen atmosphere, the solution of 4-methyl-5-(ethoxycarbonyl)thiazole was added dropwise at a rate maintaining a gentle reflux. When the addition was complete, the mixture was heated at 20 reflux for 4 hrs. After the mixture had returned to room temperature, anhydrous ether (100 mL) was added. The gray reaction mixture was hydrolyzed by addition, in small parts, of a sufficient amount of wet sodium sulfate. The reaction mixture was filtered through a sintered-glass funnel. The organic layer separated and dried over Na<sub>2</sub>SO<sub>4</sub>. It was filtered and evaporated to give desired compound as an oil; yield: 590 mg (26%).

25

**3-(2-Phenyl-2-oxoethyl)-4-methyl-5-(hydroxymethyl)thiazolium chloride.**

The neat reaction of 4-methyl-5-(hydroxymethyl)thiazole (590 mg, 4.57 mmol) and 2-chloroacetophenone (710 mg, 4.59 mmol) was heated at 110°C. The mixture solidified within 15 minutes. Acetonitrile (10 mL) was added and the mixture refluxed for another 30 3 hrs. It was cooled to room temperature and tert-butyl methyl ether (5 mL) was added

and the reaction mixture was left overnight at room temperature. The product crystallized was filtered and washed well with a mixture of hexanes: EtOAc (1:1, v/v) and dried. It was recrystallized from a mixture of acetonitrile/ethanol/ tert-butyl methyl ether; yield 130 mg (10%); mp.240-242°C (dec.).

5

**EXAMPLE 6. 3-[2-(Disubstituted-dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide.**

**2-Bromo-2',4'-dihydroxyacetophenone.**

Copper (II) bromide (6 g, 26.9 mmol) was suspended in ethyl acetate (50 mL) and 2',4'-dihydroxyacetophenone (2 g, 13.1 mmol) dissolved in chloroform (20 mL) was added to the suspension. The reaction mixture was refluxed for 8 hrs. and filtered hot through celite pad. The filtrate was evaporated to dryness to give crude oil (3.0 g, 96%). The NMR spectrum and TLC [silica gel, Hexanes:EtOAc (1:1, v/v)] was in agreement with the desired product. It was used as such in the next step of the reaction without further purification.

This method was used to prepare:

- (i) 2-Bromo-3',5'-dihydroxyacetophenone from 3',5'-dihydroxyacetophenone and copper (II) bromide.
- (ii) 2-Bromo-2',5'-dihydroxyacetophenone from 2',5'-dihydroxyacetophenone and copper (II) bromide. Yield: 2.99g; 99%

**3-[2-(2,4-Dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide.**

The neat mixture of 2-bromo-2',4'-dihydroxyacetophenone (3 g, 13 mmol) and 4,5-dimethylthiazole (1.71 g, 13.3 mmol) was heated at 110°C for 3 hrs. It was dissolved in acetonitrile (15 mL) and cooled to room temperature. Tert-butyl methyl ether (5 mL) was added and the reaction mixture kept at room temperature overnight. The product crystallized was filtered, washed well with a mixture of acetonitrile and tert-butyl methyl ether (1:1, v/v) and dried. It was recrystallized from a mixture of methanol and a few drops of water. Yield: 2.5 g (50%); mp. 257-260°C (dec.).

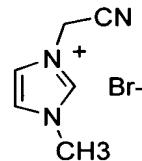
This method was used to prepare:

(i) 3-[2-(3,5-Dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide in 55% yield from 2-bromo-3',5'-dihydroxyacetophenone and 4,5-dimethylthiazole; mp. 257-5 258°C. Yield: 2.05 g (21%).

(ii) 3-[2-(2,5-Dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium bromide in 57% yield from 2-bromo-2,5-dihydroxyacetophenone and 4,5-dimethylthiazole; mp. 231-232°C. Yield: 4.03 g (52%).

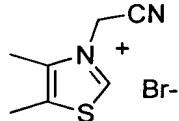
(iii) 3-[2-(3,4-Dihydroxyphenyl)-2-oxoethyl]-4,5-dimethylthiazolium chloride in 60% 10 yield from commercially available 2-chloro-3',4'-dihydroxyacetophenone and 4,5-dimethylthiazole; mp. 260-263°C (dec.); yield: 3.9 g (48%).

**EXAMPLE 7.** Preparation of 1-methyl-3-(cyanomethyl)imidazolium bromide



15 A mixture of 1-methylimidazole (1 g, 12.2 mmol) and bromoacetonitrile (1.46 g, 12.2 mmol) were combined and stirred. An exothermic reaction was produced and the product precipitated from the reaction mixture. After cooling the reaction mixture is allowed to cool to room temperature acetonitrile (CH<sub>3</sub>CN) (2 mL) is added. The crude product is recovered by filtration and washed with additional CH<sub>3</sub>CN. The crude 20 product is dissolved in H<sub>2</sub>O, treated with decolorizing carbon and evaporated in vacuo to dryness. The product is further purified by recrystallization from a mixture of ethanol EtOH, CH<sub>3</sub>CN and diethyl ether to yield 1-methyl-3-(2-cyanomethylene)-imidazolium bromide as a white crystalline solid: mp 165-167 °C.

25 **Example 8.** Preparation of 3-(cyanomethyl)-4,5-dimethylthiazolium bromide

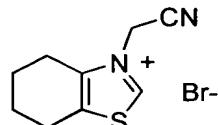


A mixture of 4,5-dimethylthiazole and bromoacetonitrile were heated with stirring at 95 °C for 1 hour. The product precipitated from the mixture within 30

minutes. After cooling to room temperature, the product a solution of 30% v/v of diethyl ether:  $\text{CH}_3\text{CN}$  (10 mL) was added with stirring. The crude product was recovered by filtration, and recrystallized from a mixture of EtOH and  $\text{CH}_3\text{CN}$  to yield 2.136 g of 3-(cyanomethyl)-4,5-dimethylthiazolium bromide as needles: mp 184-186 °C (dec.).

5

**Example 9.** Preparation of 3-(cyanomethyl)-4,5-cyclohexenothiazolium bromide



A mixture of thioformamide (0.8 g), 2-chlorocyclohexan-1-one (1.73 g),  $\text{MgCO}_3$  (1.5 g) was refluxed in dioxane (12 mL) for 30 h. The reaction mixture was evaporated in vacuo, and the concentrated poured into diethyl ether (30 mL). The resulting ethereal solution was washed with 1% NaOH solution (3 x 15 mL). The combined NaOH solution was back extracted with diethyl ether. The ether layers were combined, washed with saturated NaCl sountion until neutral, and then dried over  $\text{Na}_2\text{SO}_4$ . The ethereal solution was evaporated in vacuo to afford 1.02 g of 4,5-cyclohexenothiazole.

15 A mixture of 4,5-cyclohexenothiazole (1 g, 7.2 mmol) and bromoacetonitrile (0.863 g, 7.2 mmol) were heated at 120 °C for 1 h. After cooling the reaction mixture was treated with a solution of 30% diethyl ether in  $\text{CH}_3\text{CN}$  (10 mL). The product was recovered by filtration and washed with additional 30% diethyl ether in  $\text{CH}_3\text{CN}$ . The product was recrystallized from a mixture of EtOH and  $\text{CH}_3\text{CN}$  to yield 0.752 g of 3-(cyanomethyl)-4,5-cyclohexenothiazolium bromide as a crystalline solid: mp 215-217 °C (dec.).

The preparation of 3-(2-cyanomethyl)-4,5-cyclopentenothiazolium bromide from 2-chlorocyclopentan-1-one is conducted as in the above procedure.

25 **Example 10.** Preparation of 3-[2-(1-pyrrolidinyl)-2-oxoethyl]-1,2-dimethylimidazolium chloride

**N-(chloroacetyl)pyrrolidine**

Pyrrolidine (63.9 g, 0.9 mole) was taken up in  $\text{CH}_2\text{Cl}_2$  (640 mL) and cooled to 0 °C in a salt-ice water bath. To the stirred mixture was added chloroacetyl chloride (101.8 g in 450 mL of  $\text{CH}_2\text{Cl}_2$ , 0.9 mole) dropwise maintaining the internal temperature

below 15 °C. After adding the chloroacetyl chloride, the mixture was stirred for one hour at 5 °C. Sodium hydroxide solution (7 M, 190 mL) was added with vigorous stirring such that the inside temperature did not exceed 20 °C. The mixture was stirred for 15 minutes and the aqueous layer was separated. The organic layer was washed with 5 saturated sodium bicarbonate solution (2 x 200 mL), water (1 x 200 mL) and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was recrystallized from hexane to give 64.5 g (48.6% yield) of white plate crystals; mp 43 °C.

10 **3-[2-(1-pyrrolidinyl)-2-oxoethyl]-1,2-dimethylimidazolium chloride**

A mixture of N-(chloroacetyl)pyrrolidine (2.0 g, 13.55 mmol) and 1,2-dimethylimidazole (1.3 g, 13.5 mmol) were heated neat at 110 °C for 3 hours. To the reaction mixture was added acetonitrile (5 mL), and heating was continued for 20 minutes. Tert-butyl methylether (10 mL) was added, and the resulting mixture was allowed to stand at room 15 temperature overnight. The product was recovered by filtration, and washed with a mixture of tert-butyl methyl ether and acetonitrile (7:3 v/v, 50 mL). The crude product was recrystallized from a mixture of acetonitrile and tert-butyl methyl ether to obtain 1.23 g (41%) of a white solid; mp 191-193°C.

20 **Example 11. Preparation of 1-butyl-3-aminoimidazolium mesitylene sulfonate**

An ice-cold solution of 1-butylimidazole (7.0 g, 16.30 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (35 mL) was treated dropwise with a solution of O-mesitylene sulfonylhydroxylamine (17.8 g, 16.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (70 mL). After stirring for 6 hours in the ice-bath, ether (210 mL) was added with stirring over the course of 1 hour. 25 The resulting mixture was allowed to stand at -16 °C overnight. The product was recovered by filtration, and washed with a mixture of CH<sub>2</sub>Cl<sub>2</sub>: ether (3:1 v/v) to yield a white amorphous powder; 16.70 g. The crude product was recrystallized from a mixture of CH<sub>2</sub>Cl<sub>2</sub> (80 mL) and ether (80 mL) to give 12.40 g; mp 71-73 °C.

30 **Definition**

**Heterocycle.** Except where heteroaryl is separately recited for the same substituent, the term "heterocycle" includes heteroaryl.

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually 5 indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference herein in its entirety in the manner described above for publications and references.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations in the 10 preferred devices and methods may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the claims that follow.

100 90 80 70 60 50 40 30 20 10